Drug Development & Delivery

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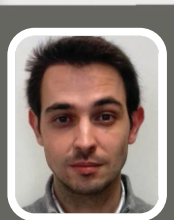
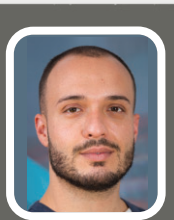
ASDs: From API to Tablets

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



Paulo Lino, PhD
ASDs: Increasing Solubility From API to Tablets

Kaiser Aziz, PhD
FDA's Quality Risk Management Approach to New Drug Applications



Rafael Miñana, PhD
Zebrafish in Preclinical Drug Development - A Small Fish With Big Returns

IN THIS ISSUE

INTERVIEW WITH PCI SYNTHESIS' PRESIDENT & CEO **ED PRICE**

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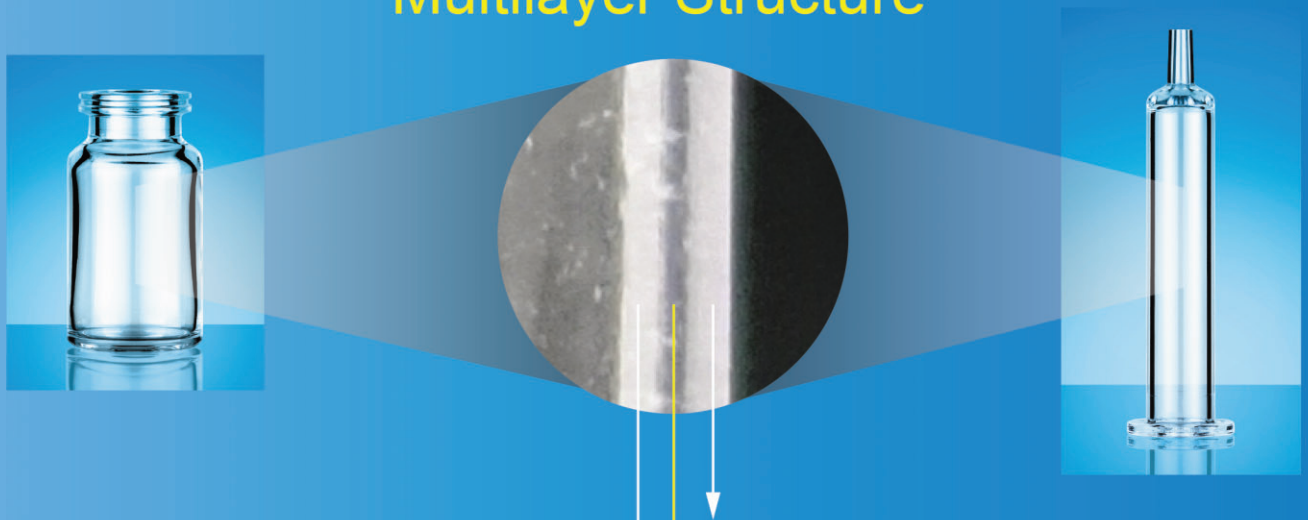

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Amorphous Solid Dispersions

"With the described approach, and using as little as 30 g API, a fully optimized ASD-based tablet prototype for a PK study can be made available within 6 weeks of initiating experimental work. The use of best-in-class methodologies ensures that scale-up risks are minimized and that the performance of the ASD formulation is maximized for optimal exposure and bioavailability."

p.32

Table of Contents

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p.47

Table of Contents

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Cambrex Completes Expansion & Manufacturing Capability Upgrades

Cambrex Corporation recently announced it has completed the expansion of a new 150-m^2 research and development laboratory at its site in Paullo, Milan, Italy. In addition, Cambrex has installed a new 12,000-liter reactor into one of its cGMP manufacturing facilities at the site.

The R&D laboratory includes both chemistry and analytical development capabilities, with the installation of semi-automated glass lined reactors, as well as analytical instruments including multiple high- and ultra-performance liquid chromatography, and gas chromatography systems, which have now been qualified and validated. To complement investments at other Cambrex sites, the new laboratory has also installed a flow chemistry system to allow for continuous manufacturing development.

The installation of the 12,000-liter reactor, along with the replacement of centrifuges with new, more efficient equipment in one of the site's seven production departments, was part of a $3-million investment to upgrade and improve the efficiency of the plant which manufactures intermediates and generic APIs under GMP conditions.

"This investment is part of our ongoing strategy to ensure that the site can adapt to the growing and evolving needs of the generic API industry," said Aldo Magnini, Managing Director, Cambrex Milan. "Investing in key technologies, such as continuous flow will allow us to look at new opportunities for the site to expand our portfolio of generic products, in a similar manner to the investment in highly potent API containment that we undertook in 2017, which allowed us to increase the number of new highly-potent oncology products in development."

Cambrex manufactures over 70 generic APIs, which are produced to cGMP standards at the Milan site, where the seven production departments are supported by a pilot plant, kilo-scale plant and development and analytical laboratories.

Cambrex is the leading small molecule company that provides drug substance, drug product and analytical services across the entire drug lifecycle. The company provides customers with an end-to-end partnership for the research, development and manufacture of small molecule therapeutics. With over 35 years' experience and a growing team of over 2,000 experts servicing global clients from sites in North America and Europe, Cambrex is your trusted partner in branded and generic markets for API and dosage form development and manufacturing.

Cambrex offers a range of specialist drug substance technologies including biocatalysis, continuous flow, controlled substances, solid state science, material characterization and highly potent APIs. In addition, Cambrex can support conventional dosage forms including solids, semi-solids and liquids and also has the capability to manufacture specialist dosage forms such as solid dose, fixed dose, pediatric, bi-layer, stick packs, topicals, controlled substances, sterile and non-sterile dose forms. For more information, visit www.cambrex.com.

Biogen Enters Agreement to Sell Its Large-Scale Biologics Manufacturing Site

Biogen recently announced it has entered into a share purchase agreement with FUJIFILM Corporation under which Fujifilm will acquire the shares of Biogen's subsidiary, which holds Biogen's biologics manufacturing operations in Hillerød, Denmark, for up to $890 million in cash, subject to minimum purchase commitment guarantees and other contractual terms. The approximately 800 employees at the Hillerød subsidiary are expected to continue employment under Fujifilm ownership.

As part of the proposed transaction, Biogen also announced it will enter into manufacturing services agreements with Fujifilm. Following the completion of the transaction, Fujifilm will use the Hillerød site to produce commercial products for Biogen, such as TYSABRI, as well as other third-party products.

"We continually evaluate our manufacturing strategy, and we believe this agreement serves the best interest of our employees, customers, partners, and shareholders," said Michel Vounatsos, Biogen's Chief Executive Officer. "As we continue to diversify our portfolio across multiple modalities and bring online our state-of-the-art manufacturing facility in Solothurn, Switzerland, we believe we have enhanced our manufacturing capabilities and capacity for biologics with this transaction. Fujifilm is a well-respected leader in manufacturing biologic products and they share our pioneering culture."

"We are proud to combine the talent and expertise of the Hillerød employees with Fujifilm's capabilities as an industry-leading contract development and manufacturing organization," said Paul McKenzie, PhD, Biogen's Executive Vice President, Pharmaceutical Operations and Technology. "We will work with Fujifilm with the goal of ensuring a smooth transition and reliable supply for our customers and patients."

The Hillerød site includes a 90,000-L biologics production facility with assembly, labeling, and packing capabilities, quality control laboratories, and warehouses. The transaction is subject to closing conditions, including customary filings and clearances under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, in the US, the Danish Competition Act, and the Korean Monopoly Regulation and Fair Trade Act. The closing of the transaction is expected to occur in the second half of 2019.

Following the closing of the transaction, Biogen will operate manufacturing facilities in Research Triangle Park (RTP), North Carolina, and Solothurn, Switzerland, which Biogen expects to be operational by the end of 2020.

Biogen expects to record a total after-tax loss in the first quarter of 2019 of approximately $130 million to $150 million, or $0.66 to $0.76 per diluted share, related to the proposed transaction. This loss includes an estimate of $120 million associated with guarantees of future minimum purchase commitments. These estimates are based on current exchange rates and business conditions.

At Biogen, our mission is clear: we are pioneers in neuroscience. Biogen discovers, develops and delivers worldwide innovative therapies for people living with serious neurological and neurodegenerative diseases.

Altimmune Announces Positive Results From NasoVAX Extension Study

Altimmune, Inc. recently announced additional positive data from a Phase 2 extension study of its NasoVAX intranasal influenza vaccine candidate. Data from this study demonstrated that 100% of the evaluated subjects remained seroprotected, and the seroconversion rate was unchanged more than one year after vaccination.

Subjects from the highest dose group of the study were invited to return as part of a study extension to evaluate the duration of immunity 1-year post-vaccination. Of 15 subjects invited, 8 returned an average of 13.5 months after vaccination. Antibody titers for all 8 subjects remained seroprotective, with a median hemagglutination inhibition (HAI) titer more than 3-times higher than generally accepted seroprotective levels. Coupled with previously demonstrated mucosal antibody and T-cell related correlates of immunoprotection, NasoVAX is well positioned to compete with other influenza vaccines currently under development.

NasoVAX, an intranasally administered recombinant influenza vaccine, uses an adenovector to achieve expression of the influenza antigen in the target cell, thereby potentially stimulating a broader and more rapid immune response than traditional influenza vaccines. Our Phase 2a trial evaluating NasoVAX started in September 2017 and was completed during 2018. Initial data, released in March 2018, indicated that

NasoVAX was well-tolerated at all doses tested. Additionally, the achievement of 100% seroprotection and statistically significant increases in mucosal antibody at two of the three dose levels studied has set NasoVAX apart from other intranasally administered vaccines. Strong T-cell responses were also observed at the highest dose. This combination of serum antibody, mucosal antibody, and T-cell responses provides the potential for improved ability to prevent infection and suggests that NasoVAX could have a greater impact on flu symptoms and shedding of the flu virus than currently approved influenza vaccines. All subjects were followed for an additional 6 months after vaccination to assess the durability of the antibody response and several subjects from the highest dose were also evaluated between 12 and 14 months after initial dosing for additional immunogenicity assessment. These new NasoVAX data, obtained from the group of 8 subjects that returned for analysis show that the immune response elicited by NasoVAX remained at seroprotective levels for at least 13 months. Durable responses on the order of 1 year are not expected from currently approved influenza vaccines and suggest that immune response induced by NasoVAX could be protective much longer than the current influenza vaccines.

NasoShield is a next-generation intranasal anthrax vaccine candidate that is intended to improve protection and safety while having favorable dosage and storage properties compared to other anthrax vaccines. By leveraging the complementary attributes of its proprietary technology platforms, Altimmune is able to design and develop immunotherapeutic products tailored to address a wide range of disease indications including both acute and chronic infections and cancer.

BioAegis Therapeutics Completes Enrollment in Phase 1b/2a Dose-Ranging Safety Study

BioAegis Therapeutics Inc. recently announced it has completed patient enrollment in its Phase 1b/2a study of recombinant plasma gelsolin (rhu-pGSN) as adjunctive therapy for patients requiring hospitalization because of Community-Acquired Pneumonia (CAP).

Severe CAP is the lead indication of this clinical-stage company that addresses infectious, inflammatory and degenerative diseases by supplementation of an endogenous protein that is depressed in these disorders. Patients were treated with recombinant human plasma gelsolin (rhu-pGSN) or a matching placebo in this blinded randomized clinical trial.

The Data Safety Monitoring Board (DSMB) met on March 4, 2019, to review the safety profile for the 12 mg/kg multiple-dose regimen (cohort 3). The review did not identify any safety concerns. Accordingly, the DSMB recommended enrollment into the last cohort at a 24 mg/kg multiple-dose level (cohort 4), and this enrollment was rapidly completed ahead of schedule. The study will include in early April, with the first results expected this summer.

Severe CAP is a leading cause of morbidity and death around the world. According to the American Thoracic Society, pneumonia mortality in the US has remained essentially unchanged since antibiotics first became widely available more than a half a century ago. Significant numbers of CAP patients develop short-term and long-term complications, placing a significant burden on the healthcare system. Survivors often require ongoing care for lingering cardiopulmonary, neurocognitive, and other functional disabilities even after hospital discharge.

BioAegis, together with investigators at Vanderbilt and Northwestern Universities along with CDC scientists, had previously demonstrated that hospitalized patients with CAP have depressed levels of plasma gelsolin at presentation. The magnitude of this depression predicts the risk of subsequent adverse clinical events.

The therapeutic efficacy of rhu-pGSN supplementation has been consistently demonstrated in greater than 25 infectious and non-infectious animal models of common diseases. Moreover, due to its host-based mechanisms of action, rhu-pGSN has been efficacious against antibiotic-resistant gram-positive and gram-negative pathogens.

Susan Levinson, PhD, Chief Executive Officer of BioAegis, said, "We are extremely excited to complete this important safety study that will ultimately lead to the filing of our US IND."

Mark DiNubile, MD, Chief Medical Officer, added "We are extremely pleased to report that cohort 4 used the highest dose ever administered to patients and no safety signals were observed at any dosing level. Now that our dose-finding trial is wrapping up, we look forward to our pivotal Phase 2b/3 study in CAP and then beyond to other infectious and non-infectious inflammatory indications."

Plasma gelsolin is an abundant circulating protein that enhances macrophage antimicrobial activity, limits the excessive spread of inflammation, and dissolves biofilm that accumulates around damaged cells. Decreased plasma gelsolin levels at presentation are not only found in CAP patients, but also in patients with diverse infectious and non-infectious inflammatory diseases, who are at high risk for developing serious complications.

Nicox Initiates Phase 2 Trial of NCX 4251 in Blepharitis

Nicox SA recently announced the initiation of a Phase 2 clinical trial evaluating NCX 4251, its novel patented ophthalmic suspension of fluticasone propionate nanocrystals, being developed as the first targeted topical treatment of the eyelid margin for patients with acute exacerbations of blepharitis. Nicox expects to report top-line results from this Phase 2 trial in the fourth quarter of 2019.

This Phase 2 multi-center, randomized, double-masked, placebo-controlled, dose-escalation, 14-day trial aims to evaluate the safety and tolerability of NCX 4251 compared to placebo in patients with acute exacerbations of blepharitis. The trial is expected to randomize approximately 30 patients in clinical sites across the US. The primary objective of this clinical trial is to select the dose(s) of NCX 4251 to advance into the next stage of development, which will be a larger Phase 2b clinical trial.

Tomas Navratil, PhD, Executive Vice President, Head of Development of Nicox, said "There is no product approved in the US solely for the treatment of blepharitis. We believe that the combination of a potent corticosteroid in our novel nanocrystal suspension together with application directly to the site of inflammation, where the disease originates, could lead to an efficacious and better tolerated product for the treatment of blepharitis."

Michele Garufi, Chairman and Chief Executive Officer of Nicox, added "Starting this second clinical program for the company, following the initiation of the NCX 470 clinical trial for the reduction of intraocular pressure in August last year, is a great achievement for our development team. With two commercial assets, two mid-stage clinical assets, and two innovative research projects we are continuing to deliver on building a unique, fully-integrated company in the ophthalmology space."

This Phase 2 trial was initiated following the US FDA acceptance of the Investigational New Drug (IND) application submitted in December 2018, ahead of the previously disclosed target date of the first quarter of 2019.

NCX 4251 is a novel patented ophthalmic suspension of fluticasone propionate nanocrystals that is being developed as the first targeted topical treatment of the eyelid margin for patients with acute exacerbations of blepharitis. Blepharitis is a common eye condition characterized by eyelid inflammation. It is being developed for application via a swab at the eyelid margin, applied directly to the site of inflammation thereby minimizing potential penetration of the drug through the cornea which can lead to the damaging side effects, such as intraocular pressure (IOP) increase, found with current topical steroids.

Fluticasone propionate, the active ingredient in NCX 4251, which has not previously been approved in a topical formulation for use in ophthalmology, has an affinity for the glucocorticoid receptor, which is approximately 10 times greater than dexamethasone, a corticosteroid commonly used in ophthalmology. Fluticasone is a glucocorticoid with potent anti-inflammatory properties that has been approved in numerous drug products over the past 20 years for the treatment of various indications including dermatology, rhinitis and asthma.


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NapaJen Pharma & Astellas Pharma Establish Research Collaboration for Discovery & Development of Novel Oligonucleotides

NapaJen Pharma, Inc. recently announced it has entered into a research collaboration with Astellas Pharma Inc. for the discovery and development of novel oligonucleotide therapeutics. Under terms of the deal, NapaJen will receive an upfront payment and research funding upon execution of the agreement. NapaJen will also be eligible for payments associated with the achievement of key research milestones.

The companies will jointly collaborate on the discovery and creation of novel oligonucleotide drug candidates utilizing NapaJen's novel delivery technology. NapaJen will be responsible for providing Astellas with a therapeutic complex combining the novel oligonucleotide with NapaJen's proprietary schizophyllan delivery vehicle for further development.

"We are very pleased to collaborate with Astellas on the research and development of novel oligonucleotide drug candidates featuring our novel, oligonucleotide delivery technology. NapaJen believes that oligonucleotide-based drugs possess tremendous therapeutic potential and commits to unlock this potential by overcoming the key delivery challenges that have limited the class to date," said Hironori Ando, Co-founder, President and Chief Executive Officer of NapaJen. "We believe that our proprietary delivery technology has the unique potential to efficiently and selectively deliver oligonucleotides to target cells, resulting in the desired therapeutic activity without troubling off-target effects."

NapaJen's proprietary drug delivery platform is designed to overcome delivery limitations that continue to present challenges for the development of oligonucleotide-based therapeutics. The primary challenge in this area is the lack of delivery technologies of oligonucleotides. Due to the high instability, low bioavailability, and poor cellular uptake associated with oligonucleotides, efficient and selective delivery technologies are critical for the development of effective and safe oligonucleotide-based therapeutics. NapaJen's novel, proprietary delivery vehicle is built upon schizophyllan, a beta-glucan that specifically binds to Dectin-1, a cell surface receptor expressed on antigen presenting immune cells, namely dendritic cells and macrophages. By complexing oligonucleotides with schizophyllan, NapaJen's delivery platform uniquely enables the efficient and selective delivery of oligonucleotides to cells playing key roles in regulating immune responses.

NapaJen Pharma, Inc. is a clinical-stage, biotherapeutics company leveraging its proprietary immune cell-targeted oligonucleotide delivery technology to develop novel immunotherapeutic agents. Founded in 2004 as a California-based biotech company, NapaJen has developed a proprietary platform technology in which oligonucleotide compounds are stably and selectively delivered to immune cells. Leveraging the versatility of the platform technology, NapaJen aims to create new oligonucleotide therapeutics in the area of immune-related conditions, such as autoimmune diseases, cancer, transplantation, and vaccine, through collaborative work with industry and academia. The company's lead therapeutic candidate, NJA-730, is an siRNA drug targeting CD40 that is currently being evaluated in a Phase 1 first-in-human clinical study in healthy volunteers. The compound is initially being developed as a potential treatment for graft-versus-host disease (GVHD), though the company believes there are numerous inflammatory immunoreactive conditions against which the compound may hold therapeutic promise. For more information, please visit www.napajen.com.

Cytovation Initiates Clinical Development Program for First-in-Class Agent for Tumor Immunotherapy

Cytovation AS recently announced the first patients have been treated in a Phase I clinical study with CyPep-1, a novel therapeutic agent being developed as a new topical therapy for HPV-induced warts. The initiation of this clinical trial marks the start of the clinical development of CyPep-1 in dermatology and oncology applications, with a Phase I trial of CyPep-1 in malignant tumors planned to start in the second half of 2019.

CyPep-1 has been designed and developed by Cytovation. It is a first-in-class lytic agent with broad application across benign and malignant tumors as a result of its novel mechanism of action. CyPep-1 selectively targets tumor cells, forming pores that destabilise and rupture the membrane to kill the cell and release neoantigens into the microenvironment and circulation, while leaving healthy cells intact. The release of neoantigens enables cytotoxic CD8 positive T-cells to mount a systemic immune response offering the possibility of long-lasting immunity against the tumor and, in the case of warts, HPV infection.

Cytovation has formulated CyPep-1 as a cream for the topical treatment of HPV-induced warts, a large medical need for which there are currently no approved drug therapies. The company has also developed CyPep-1 as a solution for intra-tumoral injection, as a single agent or in combination with checkpoint inhibitors.

Cytovation's Chief Scientific Officer, Lars Prestegarden, said "We are very pleased to achieve this first clinical milestone with CyPep-1 and to begin its formal clinical development. We have designed CyPep-1 to exploit key differences between healthy and tumor cells and have seen strong evidence of its efficacy in preclinical tumor models. We are excited to see if these results can be translated to humans both with this new trial in warts and the future trial in cancer. Both trials are expected to start during 2019 and we are looking forward to reporting first findings later in the year."

The clinical trial with CyPep-1 is a randomized, placebo-controlled, double-blind Phase I study. The study is being conducted at the Centre for Human Drug Research (Leiden, the Netherlands) and will enrol 58 patients with cutaneous warts. Results are expected in the late 2019.

Warts are benign skin tumors caused by Human Papilloma Virus (HPV). There are over 100 strains of HPV which can cause several types of warts (common, flat, plantar, genital). Warts are highly contagious and affect up to 12% of the population and up to 20% of children. Traditionally wart elimination occurs through dermal abrasion via cutting, freezing or different OTC products, but there is no cure and reoccurrence is common. There is a large medical need and commercial opportunity in excess of $4 billion per year for a safe and effective treatment that eliminates warts and cures the HPV infection.

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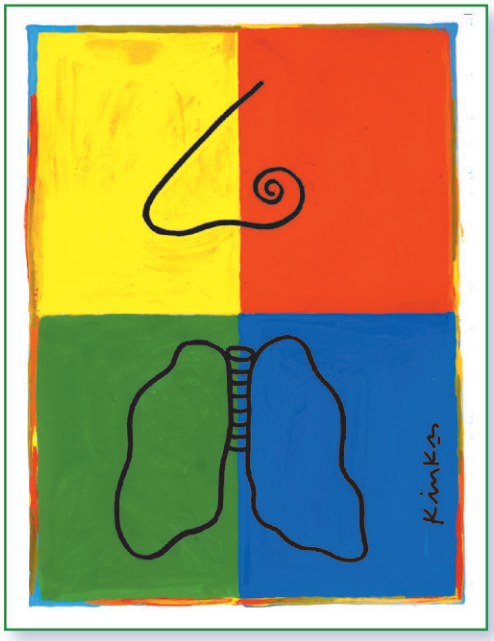
Respiratory Drug Delivery



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Formulation Forum

Revitalization of Older Drug Products Using Innovative Formulation Technologies by 505(b)(2) Regulatory Pathway

By: Jim Huang, PhD, Founder & CEO, Ascendia Pharmaceuticals

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"Every once in a while, a new technology, an old problem, and a big idea turn into an innovation" - Dean Kamen, inventor of the Segway

More than 50% of approved drugs on the market contain poorly water soluble APIs, which typically are associated with poor bioavailability, suboptimal drug delivery, ineffective drug efficacy, and side effects.[1] This creates a huge opportunity in generating 505(b)(2) products, which address unmet medical needs by applying formulation technologies to overcome those difficulties.

A key feature of the 505(b)(2) pathway is the 505(b)(2) sponsor can rely upon clinical data or literature produced by other companies. The 505(b)(2) pathway allows manufacturers to acquire FDA approval without performing all the work required with a traditional NDA. The 505(b)(2) strategy can be an option to improve existing drug products with a new indication, dosage form, dosing regimen, strength, combination with other products, new route of administration, elimination of food effect, switching from a prescription drugs (Rx) to an over-the-counter (OTC), non-prescription product that differs from the OTC monograph, and orphan drug indications.[2,3]

Both generic and brand companies are turning to more complex 505(b)(2) products to avoid the commoditized generic competition. Many marketed drugs have been successfully reformulated to improve efficacy, safety, and patient compliance using the NDA 505(b)(2) or 505(b)(1) regulatory pathway (Table 1). Revitalization of older marketed drug products using innovative drug delivery technologies or platforms can provide new marketing exclusivity and new patent protection, and thus offer an effective tool for product life cycle management.

While the 505(b)(2) pathway allows for using other's research results for their NDA submission, the petitioners of 505(b)(2) product still need to conduct their own research, particularly in CMC or clinical areas as required by FDA in order to gain approval.[3] 505(b)(2) drug development involves a thorough understanding of the DMPK, clinical pharmacology, biology, physical-chemical, and biopharmaceutical properties in relationship to drug dissolution, absorption, and the disposition process in the body while taking advantage of drug delivery technologies. Depending on a compound's physical, chemical, and biopharmaceutical properties, a rational formulation design should be explored with guidance from a decision tree.[4] In addition, understanding the advantages and limitations of drug delivery technologies in context with the target pharmaceutical profiles, such as drug indication, dose regime, patient population, route of administration, and patent strategy (Table 2), will be essential to a successful 505(b)(2) product development right the first time in an accelerated and quality manner.

Ascendia has developed a few patented 505(b)(2) drug products using its nano-technologies platforms to address unmet medical needs.

ASD-002 is a ready-to-use, room temperature storage, nano-emulsion parenteral form of a blockbuster oral antiplatelet medicine for the treatment of Acute Coronary Syndrome. When delivered

TABLE 1

PRODUCT	FORMULATION TECHNOLOGY	REGULATORY PATHWAY	VALUE PROPOSITION	MARKET VALUE
Abraxane for Injectable Suspension (Celgene)	nanoparticle albumin–bound paclitaxel or nab-paclitaxel	505(b)(2), New formulation, change from ethanol/surfactant solution to nanosuspension	Enhance of safety, efficacy and PK properties	1.1 billion, 2018
Restasis (Allergen)	Cyclosporine Ophthalmic Emulsion, 0.05%	505(b)(2), New indication, change route of administration	Creation of first line of treatment for dry eyes disease	1.41 billion, 2017
Neoral (Sandoz)	Cyclosporine lipid microemulsion (SEDDS)	505(b)(2), New formulation	Enhancement of bioavailability, PK profile and dose reduction	>300 million, 2000
Kaletra (Abbott)	Lopinavir/ritonavir Tablets by amorphous solid dispersion	505(b)(1), New formulation (using its own data)	Enhancement of product bioavailability, switch from refrigerated to RT storage, dose reduction	835 million, 2015

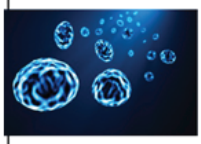
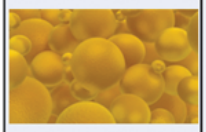
Approved reformulation product examples.

orally, there is a significant delay in the time required for the medicine to become effective - the time to reach peak concentration and therapeutic effect can require several hours. Therefore, in an acute, emergency setting, a more rapidly acting, injectable dosage form is desirable. The barrier to developing such an injectable product is due to compound's highly challenging solubility, physical form, and chemical stability properties. ASD-002 overcomes these stability and delivery challenges by stabilizing the compound by its nano-emulsion formulation.

ASD-004 is ophthalmic nanoemulsion indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Dried-eye medications, such as cyclosporine ophthalmic emulsion 0.05% is currently only available as a white, opaque emulsion (Restasis) with average of size of 100-200 nm. The market for Restasis is estimated between $870 and $900 million in worldwide sales during year of 2013, making it the best-selling ophthalmic drug by far for dried-eye disease. As described in the Restasis prescribing information, the efficacy of Restasis is moderate: only 15% of Restasis treated patients demonstrated statistically significant increases in Schirmer wetting of 10 mm versus 5% of vehicle treated patients. In clinical trials, the most common adverse reaction following the use of RESTASIS® was ocular burning (17%). Therefore, there is an unmet need to treat chronic dry eye disease that could demonstrate better response and reduced sided effects such as burning sensation and blurry vision by reducing the level of surfactant and increasing formulation clarity. Utilizing Ascendia's nanoemulsion technology platform, ASD-004 optical-clear nanoemulsion eyedrop was developed. Potential advantages of the new formulation include 1) significant reduction in droplet size to below 100 nm by Ascendia's novel formulation for ophthalmic delivery is anticipated to increase drug bioavailability and thus efficacy locally to the eyes; 2) optical clarity achieved by the new nanoemulsion approach could eliminate the blurring vision side effect; 3) reduction in surfactant level could potentially reduce or eliminate the burning sensation side effect.

ASD-005 is a liposome-like lipid nanoparticles for sustained release of a non-selective β and α adrenergic receptor blocker by the parenteral route. Currently, the drug is available only in immediate release oral tablets twice daily and oral controlled release once daily capsules with >$1 billion sale per year. There is no parenteral dosage form of available in market. Oral administration of the oral dosage form could potentially present a

TABLE 2

TECHNOLOGY	PROTOTYPE	Route of Admin.	Mechanism	APPLICATIONS
AmorSol 	AMORPHOUS NANOPARTICLES	Oral, Transdermal, Inhalation	• Solubility and dissolution rate enhancement	• Bioavailability enhancement when other technology failed for BCS II/IV • Reduction of food effect
NanoSol 	NANOPARTICLE FORMULATION	Oral, Injectable, Topical, Ocular, Nasal, Inhalation	• Enhance of dissolution and kinetic solubility by nanosizing • Achieve High loading in suspension	• Bioavailability enhancement • Stabilization of compound • Minimize food effect • Long acting injectable • Lipid nanoparticles • Injection site reaction reduction • Pediatric formulation • Biological/peptide
EmulSol 	NANOEMULSION FORMULATION	Oral, Injectable, Topical, Ocular, Nasal, inhalation	• Solubilizing of lipophilic compound • Nanosizing • Enhancement of permeability for BCS III/IV and bypass of first-pass	• Bioavailability enhancement • Solubilize and stabilize compound. • Taste masking • Injection site reaction reduction • Pediatric formulation • Biological/peptide

Understanding of formulation technology and their applicain in 505(b)(2)

challenge for patients under acute care conditions with congested hear failure or hypertension, because oral dosage forms normally have a delay in drug onset and extensive first-pass metabolism that results in an oral bioavailability of only 25%-35%; Besides, side effects such as life-threatening hypotension associated with the oral dosage form are frequently reported in patients taking those medicines. Therefore, a parenteral formulation with a rapid onset and yet a sustained-release characteristic is desirable for management of inpatients with acute cardiovascular events. Compositions containing carvedilol encapsulated in liposomes-like nanoparticles showed higher bioavailability and lower clearance rate than that of the solution form after intravenous administration. In vitro release of those liposomes in buffer solutions shows drug extended release over 48 hours, and correspondingly the in vivo animal data shows that parenteral administration of drug encapsulated in lipid materials has sustained release PK profile. ◆

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2018 Global Drug Delivery & Formulation REPORT

Two of a Four-Part Series

Part 1: A Global Review of 2018 Product Approvals

Part 2: Notable Product Drug Delivery and Formulation Approvals of 2018

Part 3: Notable Drug Delivery and Formulation Transactions and Technologies of 2018

Part 4: The Drug Delivery and Formulation Pipeline

By: Kurt Sedo, VP of Operations, and Tugrul Kararli, PhD, President & Founder, PharmaCircle

Introduction

Companies and patients continue to reap the benefits of the significant investments made in drug delivery and formulation technologies over the past few decades. Despite the absence of recent breakthrough drug delivery technologies, the pharmaceutical industry has harnessed well validated drug delivery and formulation technologies to deliver important product approvals in 2018.

One well validated technology that goes back almost 30 years with the approval of Adagen is PEGylation. Three Notable Approvals of 2018, Asparlas, Jivi, and Palynziq, all use PEGylation technologies, albeit with markedly different strategies. Asparlas, a next-generation Oncaspar, uses the same non-specific multi 5-kDa PEGylation strategy of its predecessor, but with more stable linker chemistry to improve shelf stability. Jivi, sees a 170-kDa recombinant protein conjugated with a single 60-kDa branched PEG molecule to yield the 230-kDa product. Palynziq, a 62-kDa enzyme, uses a strategy similar to that of Asparlas but with an average of nine larger 20-kDa PEG molecules. What is notable about these products is their use of multisource PEG reagents. No longer are we hearing mention of Enzon, Shearwater and their successors as technology or reagent suppliers. A technology that once commanded as much as a 7% royalty has seemingly become just another reagent sold on the basis of purity and price.

Two of the more interesting small molecule drug delivery and formulation approvals in 2018 included Inbrija and Jornay PM. Inbrija, an inhaled formulation of levodopa, represents an interesting formulation/device approach to addressing issues related to off symptoms with Parkinson's patients. Jornay PM, a colonic release formulation of methylphenidate administered in the evening, uses a totally different drug delivery facilitated dosing strategy to address the early day dosing requirements of children with ADHD.

In total, 20 products are highlighted that represent either fresh approaches or a new twist on well-understood drug delivery and formulation strategies.

Notable Drug Delivery and Formulation Approvals of 2018

Product Name	Company	Active(s)	Dosage Form	Status US	Status EU	Status JP
Allesaga Tape	Hisamitsu Pharmaceutical	Emedastine Difumarate	Transdermal Patch	Undisclosed	Undisclosed	Approved
Apadaz	KemPharm	Benzhydrocodone Hydrochloride, Acetaminophen	Oral Tablet	Approved	Undisclosed	Undisclosed
Arikayce	Insmed	Amikacin Sulfate	Inhalation Suspension	Approved	Phase 3	Phase 2
Asparlas	Servier	Calaspargase Pegol	Injection Solution	Approved	Undisclosed	Phase 3
Brilique Orodispersible	AstraZeneca	Ticagrelor	Oral Tablet	Approved	Undisclosed	Undisclosed
Buvidal	Camurus	Buprenorphine HCl	Injection Solution	Tentative Approval	Approved	Undisclosed
Dextenza	Ocular Therapeutix	Dexamethasone	Ophthalmic Insert	Approved	Undisclosed	Undisclosed
DSUVIA	AcelRx Pharmaceuticals	Sufentanil	Sublingual Oral Tablet	Approved	Approved	Undisclosed
Epidiolex	GW Pharmaceutical	Cannabidiol	Oral Solution	Approved	Registration	Undisclosed
Inbrija	Accorda Therapeutics	Levodopa	Inhalation Powder in Capsule	Approved	Registration	Undisclosed
Jivi	Bayer Healthcare	Damoctocog Alfa Pegol	Injection Lyophilized Powder for Solution	Approved	Approved	Approved
Jornay PM	Ironshore Pharmaceutical	Methylphenidate Hydrochloride	Oral Capsule	Approved	Undisclosed	Undisclosed
Licart	Institut Biochimique	Diclofencac Epolamine, Heparin (enhancer)	Topical Patch	Approved	Undisclosed	Undisclosed
Makena (SC Auto-injector)	AMAG Pharmaceuticals	Hydroxyprogesterone Caproate	Injection Solution	Approved	Undisclosed	Undisclosed
ONPATTRO	Alnylam Pharmaceuticals	Patisiran	Injection Solution	Approved	Approved	Registration
Palynziq	BioMarin Pharmaceutical	Pegvaliase	Injection Solution	Approved	Registration	Unknown
Perseris	Indivior	Risperidone	Injection Powder for Suspension	Approved	Undisclosed	Undisclosed
Rapalimus Gel	Nobelpharma	Sirolimus	Topical Gel	Phase 3	Phase 3	Approved
Sympazan	Aquesitive Therapeutics	Clobazam	Oral Film	Approved	Undisclosed	Undisclosed
Yutiq Implant	EyePoint Pharmaceuticals	Fluocinolone Acetonide	Ophthalmic Implant	Approved	Registration	Undisclosed

Allesaga Tape

Company: Hisamitsu Pharmaceutical
Active(s): Emedastine Difumarate
Molecule Type: Small Molecule
Indication: Allergic Rhinitis
Delivery Route: Transdermal
Dosage Form: Transdermal Patch
DD Category: Patches, Drug-in-Adhesive
Dosing (Duration): Once Daily
First Approval (Country): 2018-01-19 (JP)
Technology/Provider: TransDermaSal/ Hisamitsu Pharmaceutical
Notable: A different approach to the management of allergic rhinitis by means of a transdermal patch formulation.

Asparlas

Company: Servier
Active(s): Calaspargase Pegol-mknl
Molecule Type: Protein Polymer Conjugate
Indication: Acute Lymphoblastic Leukemia
Delivery Route: Injection (Infusion IV)
Dosage Form: Injection Solution (Refrigerated)
DD Category: Conjugates, PEG Polymer
Dosing (Duration): No More Frequently than 21 Days
First Approval (Country): 2018-12-20 (US)
Technology/Provider: Enzon PEGylation Linker Technology/Belrose Pharma
Notable: A next-generation Oncaspar that with improved stability. The L-asparaginase molecule (tetramer) is PEGylated with 5-kDa monomethoxypolyethylene glycol (mPEG) units using a succinimidyl carbonate (SC) linker.

Apadaz

Company: KemPharm
Active(s): Benzhydrocodone Hydrochloride, Acetaminophen
Molecule Type: Small Molecule
Indication: Acute Pain
Delivery Route: Oral
Dosage Form: Oral Tablet
DD Category: Conjugates, Small Molecule
Dosing (Duration): 4 to 6 Times Daily
First Approval (Country): 2018-02-03 (US)
Technology/Provider: Ligand Activated Therapy/ KemPharm
Notable: Apadaz builds on the success of other prodrug CNS products attempting to discourage abuse by injection and insufflation using a prodrug approach rather than physical abuse-deterrent technologies. The FDA, while approving the product, did not judge the product to deter abuse by the oral or nasal routes of administration.

Brilique Orodispersible Tablets

Company: AstraZeneca
Active(s): Ticagrelor
Molecule Type: Small Molecule
Indication: Acute Coronary Syndrome
Delivery Route: Oral
Dosage Form: Oral Tablet
DD Category: Oral Dispersible
Dosing (Duration): Twice Daily
First Approval (Country): 2018-05-18 (EU)
Technology/Provider: Undisclosed
Notable: A simple formulation enhancement to improve acceptance and compliance in a more elderly patient group.

camurus®

Buvidal

Company: Camurus
Active(s): Buprenorphine HCl
Molecule Type: Small Molecule
Indication: Opioid Dependence
Delivery Route: Injection (IM)
Dosage Form: Injection Solution
DD Category: Biodeg Gel/Suspension, Prefilled Syringes
Dosing (Duration): Weekly, Monthly
First Approval (Country): 2018-11-21 (EU)
Technology/Provider: FluidCrystal Depot/Camurus
Notable: Available in once-weekly and once-monthly dosage forms Buvidal represents the first approval of a long-acting treatment for opioid dependence in the EU.

GW pharmaceuticals

Epidiolex

Company: GW Pharmaceutical
Active(s): Cannabidiol
Molecule Type: Small Molecule
Indication: Lennox-Gastaut Syndrome
Delivery Route: Oral
Dosage Form: Oral Solution
DD Category: Oral
Dosing (Duration): Twice Daily
First Approval (Country): 2018-06-25 (US)
Technology/Provider: None
Notable: Developed as a simple sesame formulation, Epidiolex provides a benchmark for companies developing cannabis-based products in terms of regulatory authority (FDA & DEA) accommodations.

Ocular Therapeutix™

Dextenza

Company: Ocular Therapeutix
Active(s): Dexamethasone
Molecule Type: Small Molecule
Indication: Post-Operative Pain
Delivery Route: Ophthalmic
Dosage Form: Ophthalmic Insert (Refrigerated)
DD Category: Ocular Implants/Rods/Microcapsules
Dosing (Duration): Single Insertion
First Approval (Country): 2018-12-03 (US)
Technology/Provider: Ocular Therapeutix Punctal Plug/Ocular Therapeutix
Notable: Dextenza is the first FDA-approved intracanalicular insert delivering dexamethasone to treat post-surgical ocular pain for up to 30 days.

BAYER Bayer HealthCare

Jivi

Company: Bayer Healthcare
Active(s): Damoctocog Alfa Pegol
Molecule Type: Protein Polymer Conjugate
Indication: Hemophilia A
Delivery Route: Injection (IV Infusion)
Dosage Form: Injection Lyophilized Powder for Solution (Refrigerated)
DD Category: Conjugates, PEG Polymer
Dosing (Duration): Once/Twice Weekly (Prophylaxis)
First Approval (Country): 2018-08-29 (US)
Technology/Provider: Not Disclosed
Notable: A PEG conjugate of Factor VIII, Jivi was approved all 3 markets in 2018. Jivi is the first B Domain Deleted PEGylated product; 60-kDa branched PEG.

Jornay PM

Company: Ironshore Pharmaceutical
Active(s): Methylphenidate Hydrochloride
Molecule Type: Small Molecule
Indication: ADHD
Delivery Route: Oral
Dosage Form: Oral Capsule
DD Category: Oral Enteric/Delayed Release, Oral Barrier Film & Microparticles, Colonic Release
Dosing (Duration): Once Daily
First Approval (Country): 2018-08-08 (US)
Technology/Provider: DELEXIS/Ironshore, Highland Therapeutics
Notable: Jornay PM provides a markedly different approach to dosing for ADHD with a colonic delayed-release formulation taken in the evening. Tmax was reached about 14 hours after dosing with only 5% of the drug available in the first 10 hours.

Caring Innovation

Licart

Company: Institut Biochimique
Active(s): Diclofencac Epolamine, Heparin (enhancer)
Molecule Type: Small Molecule
Indication: Acute Pain
Delivery Route: Topical
Dosage Form: Topical Patch
DD Category: Topical, General, Patches, Drug-in-Adhesive
Dosing (Duration): Once Daily
First Approval (Country): 2018-12-19 (US)
Technology/Provider: Hydroadhesive/Teikoku Seiyaku
Notable: A second-generation nonsteroidal anti-inflammatory in patch presentation formulated with heparin to improve local absorption.

ONPATTRO

Company: Alnylam Pharmaceuticals
Active(s): Patisiran
Molecule Type: siRNA
Indication: Amyloidosis
Delivery Route: Injection (IV Infusion)
Dosage Form: Injection Solution (Refrigerated)
DD Category: NP lipid cationic, NP solid lipid
Dosing (Duration): Every 3 Weeks
First Approval (Country): 2018-08-10 (US)
Technology/Provider: Arbutus LNP Technology/ Arbutus Biopharma, Acuitas Therapeutics
Notable: Onpattro is the first approved siRNA product and employs a lipid nanoparticle technology that largely targets hepatocytes.

Palynziq

Company: BioMarin Pharmaceutical
Active(s): Pegvaliase-pqpz
Molecule Type: Protein Polymer Conjugate
Indication: Phenylketonuria
Delivery Route: Injection
Dosage Form: Injection Solution
DD Category: Conjugates, PEG Polymer, Prefilled Syringes
Dosing (Duration): Daily to Weekly
First Approval (Country): 2018-05-24 (US)
Technology / Provider: PEGylation / Biomarin Pharmaceuticals
Notable: A PEGylated version of an enzyme that involves nine separate 20-kDa PEG molecules [N-hydroxysuccinimide (NHS)-methoxypolyethylene glycol (PEG)]. PEGylation continues to be the preferred polymer for half-life extension and immunogenic reduction with protein-based molecules.

Perseris
Company: Indivior
Active(s): Risperidone
Molecule Type: Small Molecule
Indication: Schizophrenia
Delivery Route: Injection (SC)
Dosage Form: Injection Powder for Suspension (Refrigerated)
DD Category: Biodeg Gel/Suspension
Dosing (Duration): Once Monthly
First Approval (Country): 2018-07-27 (US)
Technology/Provider: ATRIGEL/Tolmar
Notable: The first subcutaneous, long-acting, formulation of a second-generation antipsychotic using the well-validated Atrigel technology.

Rapalimus Gel
Company: Nobelpharma
Active(s): Sirolimus
Molecule Type: Small Molecule
Indication: Tuberous Sclerosis Complex
Delivery Route: Topical
Dosage Form: Topical Gel (Refrigerated)
DD Category: Topical Gel
Dosing (Duration): Every 12 Hours
First Approval (Country): 2018-03-23 (JP)
Technology/Provider: Not Disclosed
Notable: Using relatively unremarkable topical formulation technology and a well-validated multisource active (sirolimus), Rapalimus addresses a rare genetic disease with few therapeutic options.

Sympazan
Company: Aquesitive Therapeutics
Active(s): Clobazam
Molecule Type: Small Molecule
Indication: Lennox-Gastaut Syndrome
Delivery Route: Oral
Dosage Form: Oral Film
DD Category: Rapidly Disintegrating Films
Dosing (Duration): Once/Twice Daily
First Approval (Country): 2018-11-01 (US)
Technology/Provider: PharmFilm/Aquesitive, MidaSol Therapeutics
Notable: One of the very few rapidly disintegrating films approved in 2018, Sympazan is well suited for the approved pediatric population of 2 years and above.

Yutiq Implant
Company: EyePoint Pharmaceuticals
Active(s): Fluocinolone Acetonide
Molecule Type: Small Molecule
Indication: Uveitis
Delivery Route: Implant (Intravitreal)
Dosage Form: Ophthalmic Implant
DD Category: Ocular Implants/Rods/Microcapsules, Injectable Non-biodeg. Polymeric Implants
Dosing (Duration): 3 Years
First Approval (Country): 2018-10-12 (US)
Technology/Provider: Durasert/MEDIDUR, Psivida Ocular Implant Inserter/EyePoint
Notable: Another lower volume specialty type indication benefiting from drug delivery, a non-bioerodible intravitreal micro-insert in a drug delivery system containing 0.18-mg fluocinolone acetonide, designed to release consistently over 36 months.

Notable Drug-Device Approvals of 2018

Arikayce

Company: Insmed
Active(s): Amikacin Sulfate
Molecule Type: Carbohydrate
Indication: Infections, Respiratory Tract
Delivery Route: Inhalation
Dosage Form: Inhalation Suspension (Refrigerated)
DD Category: NP liposome, Liquid Inhalers/ Nebulizers, Inhalation Formulations, Nebulizer
Dosing (Duration): Once Daily
First Approval (Country): 2018-09-28 (US)
Technology/Provider: PULMOVANCE Liposomal Technology/Insmed, eFlow Rapid Nebulizer (Lamira)/ Pari Pharma
Notable: An orphan product approved under the FDA's Accelerated Approval pathway, Arikayce reinforces the benefits of nebulized formulations that address locoregional indications. The combination of a vibrating mesh nebulizer with a liposomal formulation provides for effective therapy in a convenient delivery format.

DSUVIA

Company: AcelRx Pharmaceuticals
Active(s): Sufentanil
Molecule Type: Small Molecule
Indication: Acute Pain
Delivery Route: Sublingual
Dosage Form: Sublingual Oral Tablet
DD Category: Sublingual Formulations, Sublingual Delivery Devices
Dosing (Duration): As Required
First Approval (Country): 2018-06-25 (EU)
Technology/Provider: NanoTab SDA/AcelRx
Notable: DSUVIA was approved in part at the request of the US Military to address battlefield needs for a rapid acting non-injectable analgesic. The product contains a notably potent opioid with standard sublingual formulation technology packaged in a single-dose dispenser.

Inbrija

Company: Accorda Therapeutics
Active(s): Levodopa
Molecule Type: Small Molecule
Indication: Parkinson's
Delivery Route: Inhalation
Dosage Form: Inhalation Powder in Capsule
DD Category: Inhalation Formulations, DPI Dry Powder Inhalers
Dosing (Duration): Once to five times daily
First Approval (Country): 2018-12-21 (US)
Technology/Provider: ARCUS Dry Powder Formulations, ARCUS Inhaler/Accorda, Civitas, Alkermes
Notable: A novel approach to the delivery of levodopa using the lung to shorten onset of action (Tmax - 0.5 hours) and overcome issues related to variable oral absorption and first-pass metabolism.

Makena (SC Auto-Injector)

Company: AMAG Pharmaceuticals
Active(s): Hydroxyprogesterone Caproate
Molecule Type: Small Molecule
Indication: Preterm Birth
Delivery Route: Injection (SC)
Dosage Form: Injection Solution
DD Category: Autoinjectors, Disposable, Concentrated Suspension/Viscous Solution, Oil Formulations
Dosing (Duration): Weekly
First Approval (Country): 2018-02-04 (US)
Technology/Provider: VIBEX, QuickShot/ Antares Pharma
Notable: Approved as a supplement, the auto-injector provides the improved convenience of subcutaneous dosing with the simplicity of an auto-injector. This simple improvement should provide a competitive advantage following the 2018 approval of generics to the original IM vial presentation of Makena.

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DRUG DISCOVERY

Zebrafish in Preclinical Drug Development - A Small Fish With Big Returns

By: Rafael Miñana, PhD

INTRODUCTION

Recently the University of California, San Francisco (UCSF) joined forces with Barcelona, Spain-based CRO ZeClinics to commercialize a zebrafish model for childhood epilepsy that mimics the convulsive behavior and seizures associated with epilepsy. The model has a proven track record in successfully identifying new treatments against epileptic disorders and already has three compounds in Phases 1 and 2 clinical trials.

Like the researchers at UCSF, numerous others from academia and the pharmaceutical industry across the globe are using zebrafish *(Danio rerio)* to develop new drugs. Treatments are being developed more quickly to treat a broad array of therapeutic areas, including infectious diseases, Alzheimer's disease, cardiovascular diseases, neural disorders, cancers, hearing loss, and rare diseases, to name just a few. The researchers are realizing a major benefit of drug development made possible with the use of zebrafish: high-throughput screening of small molecules. These preclinical studies quickly assess toxicity and efficacy of new drugs, saving both time and money, necessities in this age of great pressure to do both.

Indeed, more than 25,000 papers have been published indicating just how important a drug discovery tool zebrafish have become - and why.

CHANGING TIMES CALL FOR A NEW WAY OF THINKING

The pharmaceutical sector has certainly undergone numerous changes in recent years, and changing times call for new ways of thinking. The development process of any drug, from early target identification to clinical testing, registration, and market approval takes at least a decade and is extremely costly. It was only a few years ago that drug manufacturers did all of their compound discovery and development in-house. Now the industry is buffeted not only by pressure to reduce development costs but is also being maligned for the high cost of prescription drugs.

Moreover, the industry faces increasing pressure from global regulatory agencies. That too, coupled with the need for speed to market, has intensified pressure on the industry. As a result, the downsizing trend took hold, leading to an unprecedented outsourcing of research to specialty contract research organizations (CROs).

The need to balance innovation flexibility with cost efficiency has never been more evident. The classic drug development model is no longer sustainable.

Recently Nature published an article about the current trend toward pharma outsourcing as headcounts are decreasing despite the fact that more and more drugs are entering the market. Particularly for the many small drug makers but also big pharma, it is difficult to have internal know-how at every step of the drug development process. By specializing in particular therapeutic areas and stages of compound development, CROs are able to provide quality services and operational flexibility at more competitive prices.

FIGURE 1

EARLIER PREDICTABILITY STEMS LOSSES

The benefits of outsourcing preclinical research are not limited to cost and workforce savings. Hiring a CRO is not a simple replacement for in-house development with external expertise. Rather, it is about risk management and early predictability. Withdrawal of potential drug candidates due to toxicity or efficacy issues after months or even years of development remains a major source of losses for the pharma industry, particularly late-phase attrition at clinical and post-market stages.[1,2]

To stem these losses, researchers are finding that preclinical assays using zebrafish funnel down large compound libraries by scrapping unsuitable candidates well before reaching more costly regulatory *in vivo* studies and clinical phases.

The trick is to generate enough biologically relevant data early on in order to improve predictability of drug targets and decrease the risk of late-phase attrition, bringing much-needed certainty for making go or no-go decisions, ultimately contributing to the sustainability of projects. Zebrafish allow pharmas to do precisely that.

The value of zebrafish research has been stymied by the general lack of awareness in the scientific community of an alternative vertebrate model. However, in the past 5 years, using zebrafish has become an increasingly prominent model for the early development of new drugs across diverse disciplines: toxicology, cancer research, human genomics, developmental biology, and many more. Zebrafish and humans share 71% of the same genes, and 82% of genes associated with human diseases.[3]

REGULATORS ARE CATCHING UP

While research conducted with zebrafish has not yet enjoyed the same level of regulatory recognition as other widespread models, regulatory bodies are catching up with recent scientific developments. Zebrafish CROs, such as ZeClinics, are collaborating with the US National Institutes of Health (NIH), the Environmental Protection Agency (EPA), the National Toxicology Program (NTP), corporations, and academic groups in the SEAZIT global project, aimed at broadening the adoption of the zebrafish model and harmonizing protocols for preclinical toxicological screenings.

To date, the groups have jointly validated a library of nearly 100 marketed products as having perfect matches with the zebrafish model. These sorts of ongoing initiatives are rapidly speeding aware-

FIGURE 2

ness among regulators of the value of faster, cheaper zebrafish models.

WHAT ZEBRAFISH LARVAE & HEN'S EGGS HAVE IN COMMON

The regulatory arena for animal models is anything but static these days. In the cosmetics field, for example, there is a European Union (EU) ban on the sale of animal-tested cosmetics, in force since 2013, which reduces testing options to in vitro models. This is not an isolated legislation with a scope limited to the cosmetics sector. Rather, it is part of a broader effort to reduce, refine, and replace the use of animals in toxicity assays (otherwise known as the 3Rs initiative). Late last year European Commissioner for Internal Market and Services, Elżbieta Bieńkowska, claimed the European Union remains "fully committed" to ending animal testing.

We fully endorse the 3Rs principles. Throughout the history of medical research, animal models have been used indiscriminately in laboratory testing. But nowadays, the scientific community and the different biopharma, cosmetic, and chemical sectors are committed to upholding higher ethical standards. Recent bans have a low impact on zebrafish testing relative to other vertebrate models for the simple reason that most of the safety and efficacy assays are carried out with zebrafish larvae at very early phases of embryonic development: from 2 to 5 days post fertilization (dpf). At those stages, organs are already fully developed, and data generated is biologically relevant, but the embryos themselves lack independent motility and rely exclusively on their yolk sac, to which they are still attached, for nutrient uptake.

For all of these reasons, Directive 2010/63/EU of the European Parliament regulates that zebrafish larvae up to 5 dpf are classified as *in vitro* models. Therefore, for all practical purposes, it is accurate to regard zebrafish embryos as 3Rs-compliant and comparable to other commonly used in vitro models, such as the hen's egg chorioallantoic membrane test (HET-CAM).

Consequently, companies that are 3Rs compliant can offer their services to clients not only in the pharma, biotech, and chemical sectors, but also the heavily regulated cosmetics sector. Other in vitro human-relevant models, such as organs-on-chip, organoids, or 3D cultures, also have great potential in combination with in silico forecasts and biologically relevant models, such as zebrafish. However, further validation is still needed before they can become a viable substitute to current animal models.

NO LONGER IMPOSSIBLE

What's required here is synergy. The ZeCardio platform serves as an example of in vivo cardiovascular work that can easily complement human cardiomyocyte research with vascular readouts.[4,5] Data such as vein and artery blood flow velocity would be impossible to obtain otherwise. Hopefully, after the 2019 Parliamentary Elections, the EU will regard zebrafish as the animal testing alternative that the Commission is calling for in order to address the 3Rs and the serious problem of late-phase attrition.

ZEBRAFISH CROS OFFER DIVERSE SERVICES

Zebrafish CROs, such as ZeClinics, offer a broad range of diverse, multidisciplinary services and expertise across numerous therapeutic areas. Therapeutic areas include, but are not limited to the follownng:

- Cardiovascular diseases
- Diseases of the Central Nervous System (CNS)
- Atherosclerosis
- Hearing Loss
- Retinal degeneration

- Muscular dystrophy
- Epilepsy
- Endocrine disruptors
- Oncology

Services include the following:

- Toxicology assays: High-throughput and organ-specific safety assessments
- Efficacy assays: Phenotypic models for biologically relevant efficacy assessments in multiple therapeutic areas
- CRISPR/Cas 9: KO and KI genetic editing to generate site-specific, a la carte mutations, to identify and validate targets, test the effect of different compounds during development, and assess phenotypic responses[6]
- Crispants: sgRNAs design and F0 physiological and phenotypical assays in just 1 week

CRISPR/CAS9: GENETICALLY MODIFIED ORGANISMS?

Earlier last year, the European Court of Justice (ECJ) ruled that gene- editing techniques, such as CRISPR/Cas9, would be regulated as Genetically Modified Organisms (GMOs). CRISPR experts at ZeClinics believe the recent ruling mostly concerns sectors other than healthcare. Why? Zebrafish gene-edited lines are employed as part of in-house preclinical assays under controlled and contained conditions, which do not fall under Directive 2001/18/EC, the piece of European legislation on the deliberate release of GMOs into the environment that is also the main source of controversy in some circles. High-precision targeted mutagenesis with CRISPR/Cas9 will remain an irreplaceable tool for the study of life-threatening diseases and the understanding at the molecular level of drug/target interactions, leading ultimately to speeding personalized medicine development.

DRUG DISCOVERY & DEVELOPMENT IS GLOBAL

The zebrafish CRO community is collaborative and international in reach. That's because sponsors choose CROs not on the basis of location but on the basis of expertise in related drug development, specific technological prowess, or experience with specific disease states. Whether the CRO is located in the US, Europe, or Asia-Pacific is far less relevant than the know-how that leads to completion of projects in a timely, cost-effective manner.

SUMMARY

In this article we explored the benefits of preclinical outsourcing, the value of zebrafish as an alternative model, as well as the challenges and opportunities of managing a highly diversified portfolio and providing customized solutions.

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BIOGRAPHY

Dr. Rafael Miñana is Services Manager of ZeClinics, a CRO that focuses on preclinical drug testing with zebrafish in multiple therapeutic areas. Dr. Miñana spends most of his day managing safety and efficacy assays, gene editing for target validation, monitoring fish facilities, and above all, coordinating a multidisciplinary team to best satisfy the requirements of their pharma, biotech, and cosmetics clients. In view of all these, it is no surprise he does not hesitate when being asked about the benefits and challenges of outsourcing drug-candidate identification and discovery.

AMORPHOUS SOLID DISPERSIONS

Increasing Solubility From API to Tablets

By: Paulo Lino, PhD, and João Henriques

INTRODUCTION

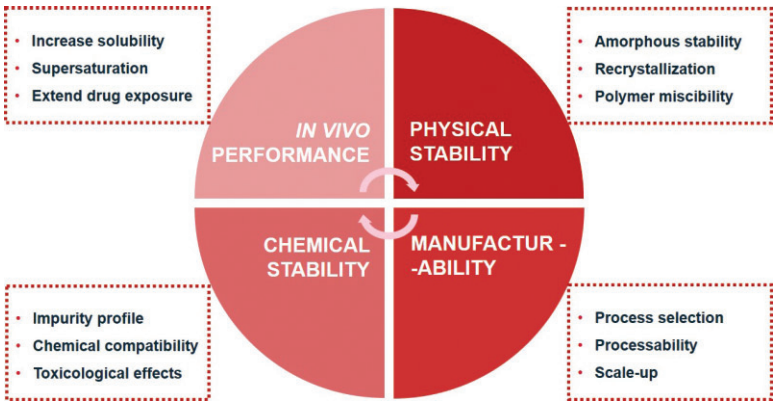
Amorphous solid dispersions (ASDs) have become an established platform to address bioavailability challenges due to low aqueous solubility of new drugs in the pharmaceutical pipeline.[1] Despite the clinical and commercial success of ASDs, with 24 FDA-approved therapies, there are perceived risks that may drive the selection of "simpler" enabling platforms.[2] These include lack of previous experience with ASDs, concerns on physical stability, and the apparent complexity involving the development of ASD formulations. Here, we will discuss and highlight the most relevant aspects of the latter.

The following discusses the main development goals (Figure 1) and presents a framework for a streamlined development of ASD formulations by spray drying (SD). The use of *in-silico* tools and miniaturized techniques in ASD formulation screening is exemplified as well as the objective gains in development time and material consumption. Also highlighted is the importance of a thorough understanding of the mechanisms and principles behind ASDs, as well as adequate analytical tools, a science-based methodology, and large-scale manufacturing know-how to achieve an optimal formulation. These aspects are essential to reduce issues and delays during early clinical stages that can ultimately impact time-to-market.

DEVELOPMENT OF ASD FORMULATIONS

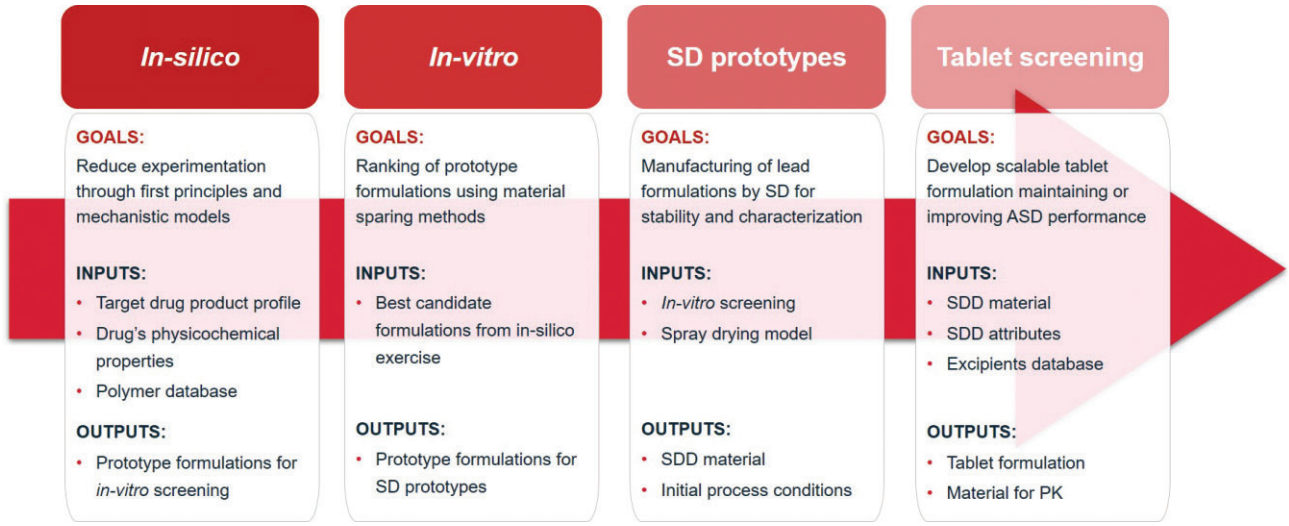
At Hovione, the development of an ASD formulation encompasses four main stages illustrated in Figure 2. The first stage consists of an *in-silico* screening in which the API properties are computed through different models to identify promising stabilizing polymers, propensity for micellization, protonation profiles, and solvent systems. An *in-vitro* screening stage follows, in which the most promising formulations are evaluated using miniaturized high-throughput tools. The final prototype formulations are selected based on physical stability, manufacturability, and performance based on biorelevant dissolution. The first spray drying prototypes are produced considering material attributes that are representative of potential clinical supplies in larger scales. Finally, the tablet formulation is developed using a data and science-based approach that enables a reduction of lab-scale experimentation, maximizing performance of the ASD and ensuring a seamless scale-up for clinical supply.

FIGURE 1



Development goals for ASD formulations

FIGURE 2



Stages in ASD formulation development

IN-SILICO SCREENING

Among the relevant API characteristics that impact ASD formulation development, solubility in aqueous media, protonation profile, and surfactant micellization propensity are key factors for determining performance and guide the initial development strategy. Cheminformatics tools can be used to generate protonation profiles and assess how the ionic species of a chemical entity is favored throughout different pH values. This will impact the API interaction with the variability of GI conditions, including food effects, and its bioavailability.

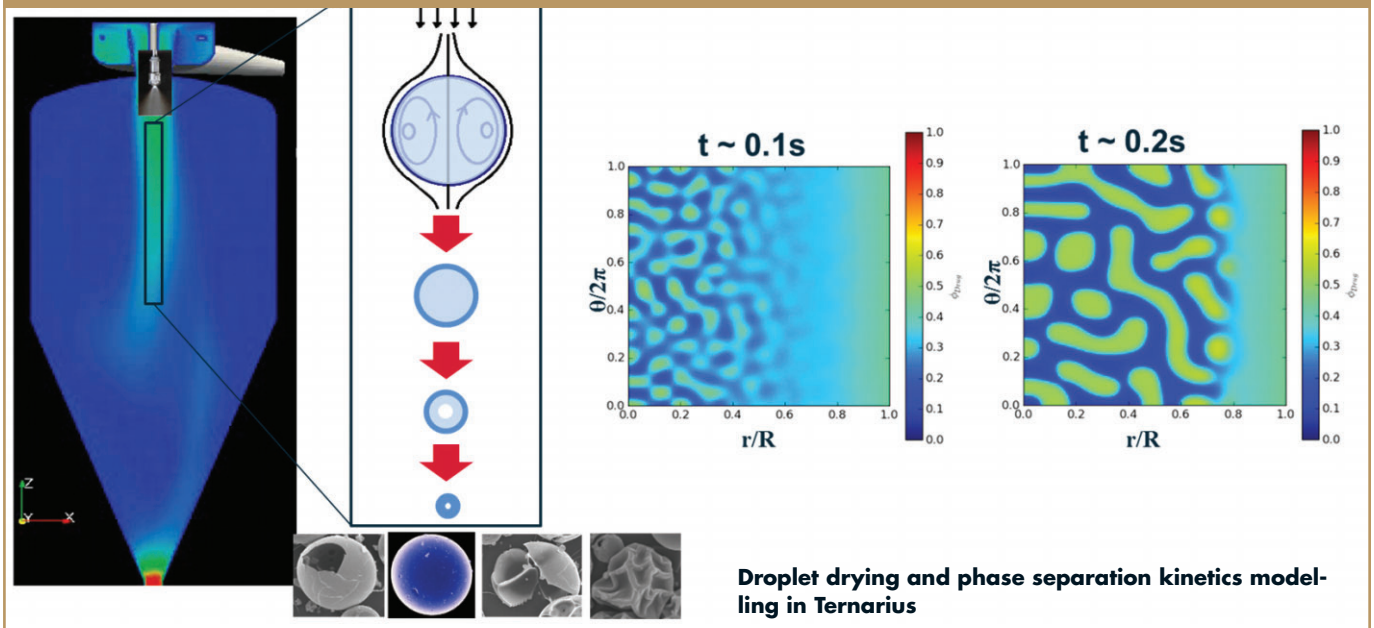
The inclusion of surfactants in a formulation may also be assessed beforehand to further enhance or extend the supersaturation of the API in the GI tract. High dose numbers are indicative of this requirement. The potential for increasing API solubility by the addition of surfactants is evaluated based on the correlation between molar solubilization capacity and micelle-water partition propensity with a drug's physicochemical characteristics, specifically logP and Mw.[3] Hence, a series of surfactants can be immediately considered in either the intermediate or final drug-product formulation.

Finally, from the variables that condition ASD formulations, the most impactful will generally be the stabilizing polymer and drug load in the ASD. This is also the most work intensive, as the multiple polymers and drug loads that may be considered amount to hundreds of combinations. Narrowing down the number of prototypes for testing is essential for API sparing, reducing development time, and ensuring that an optimal formulation is obtained. This can be achieved using computational screening tools that identify the most promising polymer and API load combinations. The platform developed by Hovione for identifying the potential of an API/polymer combination – Ternarius – conjugates the thermodynamics of mixing between ASD excipients, with the kinetics of component diffusion and evaporation rate that takes place within the SD of an atomized droplet.[4]

The thermodynamics component is based on the Flory Huggins polymer lattice theory considering both entropy and enthalpy of mixing. This generates a Gibbs free energy plot where for each polymer, the maximum drug load where mixture of components is energetically favored can be estimated. From such assessment, a small group of potential lead polymers and excipients prone to favourably interact with the API is obtained. Ternarius further expands this assessment toward the evaluation of drug-polymer phase behavior throughout the drying kinetics observed within an SD chamber where the kinetic entrapment of a drug within a polymer/excipient matrix is modelled (Figure 3). Spray drying parameters then play a key-role in accelerating or delaying the drying kinetics and typically, a worst-case slow-drying profile is considered to exclude low ranking conditions that could result in phase separation and API crystallization.

Finally, the solvent system can also play a critical role in the manufacturing and performance of an ASD formulation. To promote a homogeneous molecular dispersion of an API with the selected polymer

FIGURE 3



Droplet drying and phase separation kinetics modelling in Ternarius

and excipients, these need to be solubilized in a solvent system with a feasible solids concentration and compatible characteristics to be removed by spray drying. This can be achieved using *in silico* estimations to narrow down the solvent systems, based on both API solubility parameters and a UNIFAC model.

Overall, this streamlined *in silico* platform allows for a reduction of early stage API requirements, as only a reduced number of promising ASD formulations and solvent systems move forward to *in vitro* screening.

IN-VITRO SCREENING

The subsequent experimental stage encompasses two main dimensions, physical stability and dissolution performance of the lead ASD formulations. The experimental work is executed using high throughput and miniaturized methods. At this stage, the work consists of solvent casting experiments and supersaturation studies by solvent shift spiking in biorelevant media. Solvent casting is performed using milliliter-scale solutions aliquoted to differential scanning calorimetry (DSC) pans and polarized light microscope (PLM) glass slides. Solvent casting is a worst-case estimation of physical stability of the faster drying kinetics that occur within an SD chamber, but allows for a quick and efficient technique for differentiating ASD formulations based on their ability to maintain a single phase and avoid crystallization. DSC is used to evaluate the presence of melting peaks (indicative of crystallization) and presence of single and high glass transition temperatures characteristic of stable and homogenous ASD. PLM provides a quick qualitative assessment of the conditions that inhibit API crystallization.

In a previously published work, using both good and poor ranking polymers: HPMCAS M, PVP/VA 64, and Eudragit EPO, it was demonstrated that Ternarius provided an excellent correlation with solvent casting experiments and final itraconazole SDD physical characteristics.[4]

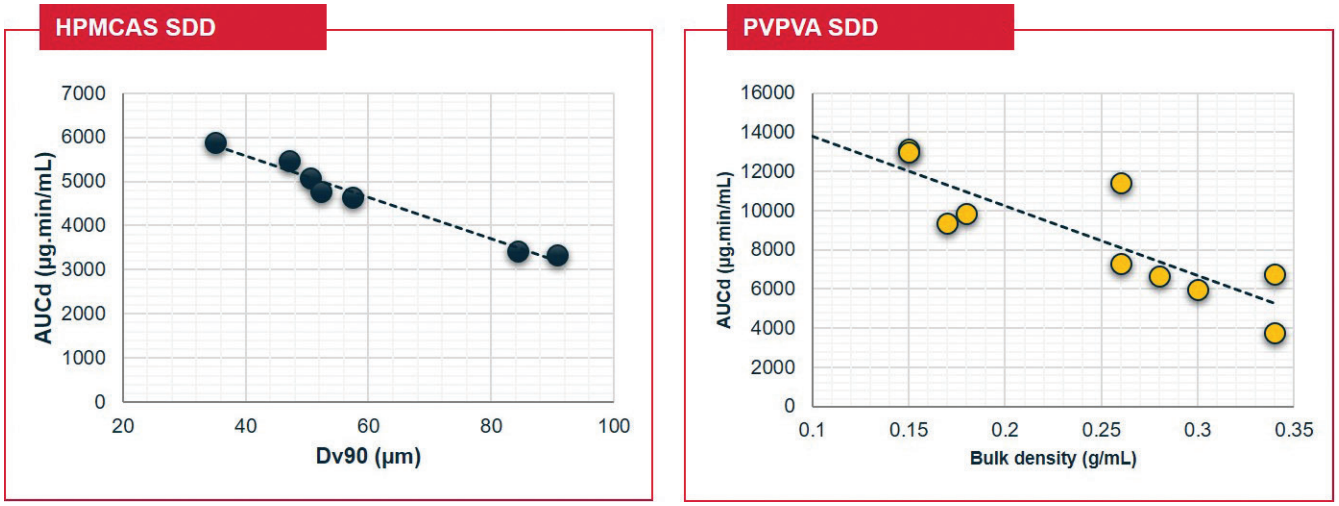
Pertaining to dissolution performance, the API amorphous solubility is initially characterized to provide insights into the underlying mechanisms involved in the drug's supersaturated state and colloidal equilibriums formed thereafter.[5] The supersaturation performance of an API is estimated by a solvent shift method aiming at the selection of conditions that extend the API supersaturation window and potentially improve its exposure within the GI tract.

The use of computational models with miniaturized *in-vitro* screening allows the definition of optimal ASD formulations with as little as 3 g API. Ranking of lab-scale screening experiments is then performed and a set of lead formulation conditions selected to move forward for spray dried dispersion (SDD) prototyping at the lab-scale.

SD PROTOTYPES – BRIDGING PARTICLE ENGINEERING & FORMULATION

SDDs are typically produced as small, low density hollow spheres, but by modulating the SD parameters, the drying con-

FIGURE 4



Correlation of dissolution performance with SDD physical attributes for HMPC AS and PVP/VA 64 based ASD

ditions can be adjusted to yield material with diverse attributes. These attributes will have a major impact on processability and performance. A formulator can engineer the SDD properties to a final target profile of choice by adjusting drying conditions. These will not only impact powder flowability and compactability, but also a product's final dissolution performance.

An illustration of the impact of SDD attributes in dissolution is provided in Figure 4. The HPMCAS-based SDD displays an inverse correlation between dissolution and particle size. Surface area, diffusion, and polymer dissolution kinetics are the main factors influencing HPMCAS dissolution. The second SDD, PVP/VA-based, exhibits an API release mainly impacted by bulk density due to its gelling nature. Disintegration and dispersion of the gelling-polymer-network act as the main bottleneck conditioning its final dissolution performance.

Prior to lab-scale prototyping, taking advantage of computational SD models, in which first principles and empirical models are applied to leverage experience in development and commercial spray drying runs, process parameters and drying conditions are selected to generate material that is representative of future clinical supplies. The use of modified, scaled-down spray dryers in combination with a comprehensive SD model for the initial prototype manufacturing is also a determining factor in the success of a development program. Hovione has developed lab-scale spray dryers that replicate the drying conditions of larger units, allowing the manufacturing of SDD with attributes representative of those in commercial scales. This is achieved by replicating gas-liquid intermixing, modulating the thermal profile, and increasing the residence time of the particles in the drying chamber to enable drying of large droplets.

This approach enables the fine-tuning and control of SD process variables and SDD characteristics toward a targeted profile of choice that can be easily scaled up. Doing so enables moving through increasing production scales with reduced risk and right-first-time clinical manufacturing without large-scale trials. Failure to account for the scale-up requirements often leads to the need of further development work or even re-formulation that may ultimately delay time-to-market. Common pitfalls during ASD development include the use of excipients and process solvents that are not amenable to large-scale processing, as well as generation of lab-scale material with properties that cannot be easily replicated at larger scales.

ASDS TABLET FORMULATION

While avoiding segregation, optimizing processability, promoting disintegration, and ensuring drug release are the key objectives when formulating crystalline drugs, the development of a tablet formulation for an ASD must consider an additional array of variables. From a performance perspective, this corresponds to ensuring that the performance gains obtained in the SDD formulation are kept or improved. Supersaturation must be promoted and maximized, but also maintained throughout the absorption window to ensure adequate exposure.

Drug Load

An ASD-based tablet will generally have a dominant influence of the SDD in the tablet properties. The stabilizing poly-

mer in the dispersion will range from 20% to 80% of the intermediate composition. This reduces the applicability of platform-based approaches and leaves little room to improve blend properties through the addition of excipients without compromising patient compliance. The use of an excipient database coupled with mixture models for virtual formulations will aid in the definition of the expected maximum SDD load in the tablet. This approach allows maximization of the drug load in the tablet while reducing the number of prototype formulations to be tested.

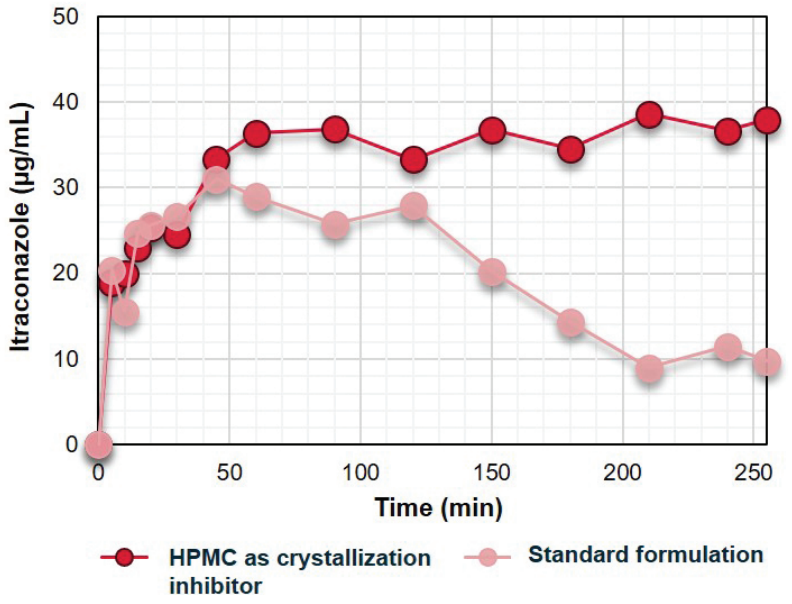
Disintegration

Promoting disintegration is a requirement for the release of the API from the tablet. The SDD polymers used to stabilize the amorphous state tend to form a gelling polymer network (GPN) that will hinder disintegration.[6] Water penetration into the tablet is reduced, and while the disintegrants may induce swelling of the tablet, a slow erosion of the gel will determine API release.

A thorough understanding of the impact of the GPN formation in tablet disintegration, as well as the influencing factors, enables the definition of strategies to improve performance without compromising patient compliance, processability and stability. Alternate disintegration strategies, including the combination of disintegrants with different mechanisms of action, may be defined to optimize tablet disintegration and effectively promote API release.

Due to the complex mechanisms surrounding disintegration, an empirical approach can be used to address this challenge. The use of empirical models coupled with a formulation database allows for a rational design of prototype formulations without compromising critical aspects of the formulation. This approach can be complemented with more selective analytical techniques to understand disintegration mechanisms and identify rate-limiting steps in the dissolution to guide additional formulation optimization.

FIGURE 5



Itraconazole: PVP/VA ASD dissolution in standard and enhanced tablet formulations

Dry Granulation

The low density, hollow spheres, obtained by spray drying will generally exhibit poor flowability. This results in variable die-filling performance in a tablet press and large weight variability. The use of a granulation step will often be required. The more common wet granulation methods are avoided with ASDs due to the risk of crystallization; dry granulation methods, specifically roller compaction, is usually preferred.

Dry granulation will improve flowability and allow a robust compression operation. On the other hand, the compressibility of the blend will be reduced upon the initial compaction of the roller compaction. The polymers present in the SDDs present good compressibility, but the decrease in compressibility may change the required solid fraction to achieve the target tensile strength up to a point when disintegration, and consequently drug release, are negatively impacted. The final selection of dry granulation conditions must account for all these factors, where both processability and performance are considered.

Functional Excipients for ASD Formulations

Addition of functional excipients should be considered when the dissolution performance is below required. Excipients to be assessed for ASD formulations include surfactants, crystallization/precipitation inhibitors, and permeation enhancers. Selection of surfactants will follow a methodology similar to the one described for the ASD screening stage. Precipitation inhibitors may include polymers from the ASD screening stage that were excluded

due to low physical stability of the ASD. An example of the use of crystallization inhibitors is provided in Figure 5 for an itraconazole-PVPVA ASD tablet. The addition of HPMC to inhibit crystallization extends the supersatured state and improves the potential exposure of the drug in the GI tract.

Compaction Simulation

The use of compaction simulation for material characterization and formulation screening is gaining increased attention and presents significant advantages in the case of ASD formulations. Besides the reduction in material consumption during early compression trials, the plastic-deforming polymers used for stabilizing ASDs typically exhibit a dwell-time and strain-rate dependent behavior. The behavior translates into differences in compression profiles and elastic recovery for different compression conditions.

Together with a data-based methodology for prototype formulation screening, the use of compaction simulation enables a thorough formulation development, in which a final formulation can be defined, complying with target requirements for processability and performance, while reducing the time and material required for experimental work.

MAXIMIZING DRUG EXPOSURE BY ASDS

In this paper, we described an integrated approach for the rationale and development of ASD formulations and processes. The use of science and data-based methodologies was described, as well as the advantages when compared to purely empirical or experimental approaches. The importance of integrating all steps in formulation development and taking into consideration the requirements and constraints of large-scale manufacturing was also highlighted as key for right-first-time development. The described strategy reduces overall risks in a development program and ultimately reduces time-to-market.

With the described approach, and using as little as 30 g API, a fully optimized ASD-based tablet prototype for a PK study can be made available within 6 weeks of initiating experimental work. The use of best-in-class methodologies ensures that scale-up risks are minimized and that the performance of the ASD formulation is maximized for optimal exposure and bioavailability. ◆

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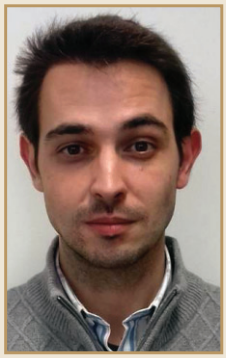
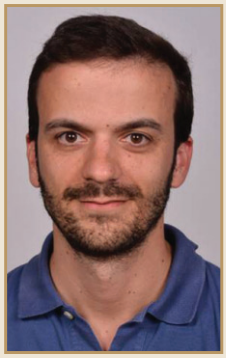
BIOGRAPHIES



Dr. Paulo Lino earned his Master's degree in Pharmaceutical Sciences at the Universidade Lusófona and his PhD and Post-Doc in Pharmaceutical Technology at the Faculty of Pharmacy, Universidade de Lisboa spanning areas from biopharmaceutical formulation/engineering, freeze-drying, and particulate polymeric drug delivery systems. In 2017, he joined Hovione at the Drug Product Development group as a Scientist and has been involved in projects that range from multivariate formulation screening and development to the tech-transfer and scale up of several solubility enhancement and particle engineering projects.



João Henriques is a Biological Engineer by training. He specialized in process monitoring and control for pharma and biopharma processes before joining Hovione in 2008 as a PAT specialist. He has been working as a Formulation and Process Development Scientist since 2013. He has supported development and validation of spray drying, jet-milling, roller compaction, and tableting projects. He is currently the Team Leader for Particle Design and Formulation at the Drug Product Development Group.

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RISK MANAGEMENT

FDA's Quality Risk Management Approach to New Drug Applications

By: Kaiser J. Aziz, PhD

INTRODUCTION

The US Food and Drug Administration (FDA) is responsible for advancing the public health by helping to speed innovations that make medicines safer and more effective and by helping the public get the accurate, science-based information it needs to use medicines to maintain and improve public health. This publication emphasizes quality risk management approaches to the development and availability of new drug information presented in the premarket applications. In 2004, the FDA provided a guidance document for innovations, challenges, and solutions for new drug products that examine the critical path needed to bring therapeutic products to completion, and how the FDA can collaborate in the process, from laboratory to production to end use, to make medical breakthroughs available to those in need as quickly as possible. In new drug applications, risk management is one of the most important features, while a sponsor's drug product development team deals with the formulation, manufacturing processes, container closure features, and user instructions. The FDA guidances help users of new drug products by providing organized data and appropriate labeling information in support of the new drug's intended clinical use.

RISK MANAGEMENT

Risk management is one of the most important tools in new drug applications to assess the risk level of a drug product (ie, physical injury and/or damage to health of the user). Risk Management promotes quality, through increased efficiency and knowledge transfer, with strong potential to reduce catch-up work done to mediate the effects of poor quality (ie, non-conformance, deviations/investigations, corrections, rework, scrap, complaints, etc). Risk management helps to provide rationale for not spending time and resources on low risk activities, rather focusing on the things that are really important. Risk management is highly beneficial in that it can also be used to identify and justify process improvements (ie, process validation). Additionally, the use of risk assessments can allow pharmaceutical manufacturers to explore weaknesses and to construct scientific and data based rationales. The risk management process is an ongoing process, which requires documentation throughout design development and product life cycle (Figure 1). Risk management is a process consisting of well-defined steps that, when taken in sequence, supports quality of the product as intended. Risk assessment tools can also provide a means for the validation of processes (such as the approach referred to in the FDA Code of Federal Regulations, CFR 21, Part 820, Quality Management Regulations).

Risk management process includes the following elements:

- Risk analysis
- Risk evaluation
- Risk controls
- Production and post-production data maintenance

This publication emphasizes quality system risk management approaches to the development, manufacturing, and new drug applications (NDAs) approvals.

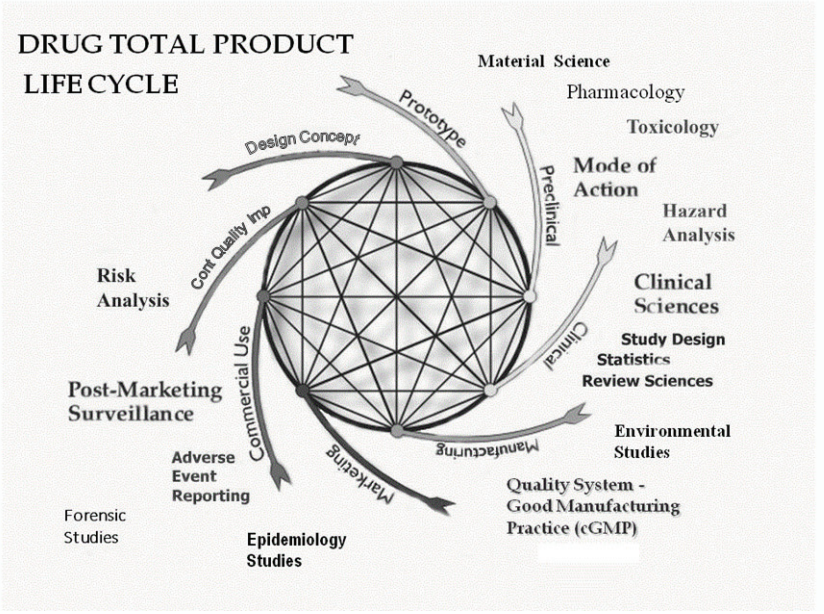
Quality risk management (QRM) is a critical component of an effective quality system framework. It can, for example, help guide the setting of specifications and process parameters for drug manufacturing, assess and mitigate the risk of changing a

process or specification, and determine the extent of non-conformance investigations and corrective actions.

DRUG PRODUCT DEVELOPMENT

The drug product development section of an NDA contains information on the development studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions are appropriate for the intended purpose specified in the NDA. The studies included in this section are in addition to those routine control tests conducted on a lot-by-lot basis according to specifications (ie, release testing and stability testing). A brief description of each of the components of this development section is indicated according to ICH Q8 guidance. A brief summary describing the development of the drug product taking into consideration the proposed route of administration and intended clinical use is provided as part of the NDA. Any parameters relevant to the performance characteristics or manufacturability (ie, active ingredients, release testing, stability, etc) are addressed in the NDA. Physicochemical and biological properties, such as pH, osmolarity, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, potency, and /or immunological activity can be essential elements of drug product performance characteristics. For development activities that include quality-by-design (QbD) approaches and description of testing technologies and summary results are important elements of product development and quality system control.[1-7]

FIGURE 1



Drug Total Product LifeCycle

QUALITY BY DESIGN (QBD)

The concept of quality by design (QbD) is related to designing and developing a drug product and associated production processes that are used during product development to ensure that the product consistently attains a predefined quality at the end of the manufacturing process.[1] QbD, along with an effective quality system, provides the framework for the transfer of product knowledge and process understanding from drug development to the commercial manufacturing processes and for post-development changes and optimization. This is the main concept within the FDA's cGMP Quality System guidance on process validation.[2,3,5]

The FDA issued a final report on Pharmaceutical cGMPs for the 21st Century-A Risk-based Approach. This report resulted in modernization of the FDA's approach with a revised framework of science-based regulation of drugs quality that encompass quality systems and risk management. This report is intended for pharmaceutical companies to innovate and adopt state-of-the-art science and technologies applicable to their product's manufacturing critical control points and intended clinical use. Critical quality attributes (CQA) of manufacturing processes associated with the drug product are physico-chemical, biological, or microbiological limits, ranges, or distribution to ensure the desired product quality. Critical process parameters (CPP) are those parameters whose variability has an impact on CQA, and therefore require monitoring to ensure that the manufacturing process produces the desired quality.[2-6] According to ICH Q8, design space involving multidimensional combination and interaction of input variables (ie, drug material attributes) and process parameters that have been demonstrated to provide assurance are not considered as a change; however, movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval review.[2,6] Design space is proposed by the NDA's sponsor and is subject to regulatory assessment and ap-

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proval. Design controls are a planned set of controls derived from a product and process that is related to drug substance and drug product materials, pre-clinicals, clinicals, manufacturing equipment operating conditions and space, finished product specifications, and continuous quality control as described in Figure 1. In a typical NDA, Drug Product Life Cycle (DPLC) covers all phases in the life of a drug product from the initial development through marketing until the product's discontinuation.[2,4-7] QbD approach incorporates the philosophy of "built-in-quality" whereby the drug substance/drug product, and the respective manufacturing process and controls are designed and developed through systematic understanding and controlling of the critical variables affecting the product quality based on HACCP principles in conformance with quality target product profile (QTPP).[2] QTPP covers a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product described in the NDA.[3-7]

CORRECTIVE & PREVENTIVE ACTIONS (CAPA) FOR THE FDA-REGULATED NDAS

Pharmaceutical companies that manufacture drug products and submit NDA's for FDA approval are subjected to pre-New Drug Application Approval Inspection and it is very important for companies to consider the Code of Federal Regulations that may apply to the company's premarket applications.[3-7] The FDA filing and premarket applications consist of the following categories:

1. Investigational New Drug Application (IND)
2. New Drug Application (NDA)
3. Abbreviated New Drug Application (ANDA)

For a drug manufacturer to introduce a product in the market for human use, a regulatory procedure is applicable. This procedure includes preclinical and clinical studies (good laboratory practice-GLP and good clinical practice-GCP studies).[3-7] Much of the Good Clinical Practices (GCP) requirements are derived from 21 CFR Part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals.[1,3,5] These GCP requirements also include considerable input from International initiatives and guidances. Much of the GLP and GCP requirements used in the conduct of clinical trials are "best practices" derived from regulations, guidance, and industry standards and practices.[7]

Continuous quality improvement is the result of the FDA's adoption of Industry-sponsored guidelines (ISBN 0273-3099). The FDA appears committed to support ways to promote drug development and is willing to accommodate NDA sponsors to use improved quality risk management approaches to foster innovations and improvements. These approaches help enhance the consistency and coordination of the FDA's drug quality risk management programs, in part, by integrating quality system and CAPA corrective actions into agency's regulatory processes. The ICH Q9 and Q10 were adopted by US in 2009. The FDA guidance, Quality Systems Approach to Pharmaceutical cGMPs describes the aim of the agency to help manufacturers implementing modern quality systems and risk management tools to meet the requirements of the agency's current approaches to cGMPs. The implementation of ICH Q10 throughout the product life cycle facilitates and strengthens the link between drug development and manufacturing activities.[7] In addition to ICH Q10, the FDA adopted industry- sponsored guidelines for quality risk management. This current emphasis toward a risk based approach has been projected by adopting ICH Q9 and Q10 in addition to WHO Technical Report Series No. 908, 2003, Annex 7- Application of Hazard Analysis-Critical Control Points (HACCP) Methodology.[2,6] HACCP Risk management techniques can be applicable to establish manufacturing critical limits, critical control points monitoring, corrective actions, and record-keeping verification procedures.[2,5,6] HACCP is a risk management system in which product or process safety can be addressed through the analysis and control of biological, chemical, and physical hazards from incoming raw materials from production to manufacturing, distribution to use of the finished product. The HACCP system identifies specific hazards and measures for their control.[2,6] Examples of hazards within the pharmaceutical setting are: environmental aspects of the facility (ie, environmental conditions, hygiene aspects); material flow; manufacturing steps; personnel hygiene gowning and technical aspects relating to process design. HACCP is a tool that is used to focus more on prevention and can be used to reduce the reliance upon in-process monitoring or end-product testing. HACCP systems are generally useful for examining changes, such as advances in equipment design, processing procedures, or technological development. The HCCP team should identify all of the hazards that may be reasonably expected to occur at each step from primary production, processing, manufac-

ture, and distribution until the point of intended clinical use.[2,4]

In conducting HACCP risk analysis, the likely occurrence of hazards and severity of their adverse health effects are considered for qualitative and quantitative analysis. In the analysis approach, critical limits are specified and validated for each critical control point (CCP) in the manufacturing process.[2,6] More than one critical limit may be required at a particular step (ie, criteria often used include measurements of temperature, time, moisture level, pH, microbial bioburden, and endotoxins).[2] Risk assessment for pharmaceuticals requires a system monitoring to control the CCP. This step may require specific corrective actions developed for each CCP in the HACCP system in order to deal with deviations when they occur. The corrective actions must ensure that CCP has been brought under control. Actions taken must also include a product risk assessment. These actions include deviation reports and a review of the effectiveness of corrective and preventive actions to provide valuable information for periodic monitoring. The advantages of the HACCP approach are that it allows for a systematic overview of the process for the evaluation of each processing step, and allows each step to examine the possible risks, and allows for the specifications of the measure required for controlling each risk. The primary objective of the HACCP system is to map out an entire process and provide a CAPA approach to quality risk management of the end product.

The FDA's QbD guidances provide essential elements for design controls from product development to the commercial manufacturing processes and for post-development changes in the drug molecules as effective as possible. The QbD approach can be maintained throughout the life cycle of the product in order to facilitate continuous quality improvement (CQI) in the final outcome of the drug product (Figure 1). In contrast, previous traditional pharmaceutical manufacturing relied heavily on end product testing, and the process typically lacked the flexibility needed to respond to variables encountered during manufacturing processes. The application of HACCP quality risk analysis approach identifies CCPs in the manufacturing process that require control monitoring because of detection of out-of-limits or drifts when they occur.[2,6] The HACCP management system provides a focus on the CCPs most likely to control product safety. This approach allows FDA reviewers and investigators to evaluate and verify that significant drug product safety hazards are properly identified and the appropriate controls are in place.

CONCLUSION

The FDA's mission is to facilitate the premarket review and evaluation of INDs and NDAs. A central theme over the past few years has been a standardized approach to evidence-based review and evaluation. The FDA emphasizes the Quality Risk Management approach to design of studies by providing oversight and objective review of risk-benefit analysis that guides the use of new drug products by providing patients organized data and appropriate labeling information in support of the new drug's intended clinical use. ◆

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BIOGRAPHY

Dr. Kaiser J. Aziz is the former Director of Mechanics and Materials Science and Associate Director of Clinical Devices for the FDA. He is currently an independent consultant for clinical research, product development, and training. He has extensive regulatory experience in medical devices and pharmaceutical premarket evaluations and approvals. He has served as an adjunct faculty in the Department of Medicine and Physiology, NIH, Graduate School, where he developed and taught courses and workshops in Applied Clinical Trials. He has been a frequent invited speaker and educator at the Center for Health Sciences, Virginia Polytechnic Institute and State University, where he developed and taught medical device and pharmaceutical risk management courses and workshops. His expertise includes FDA's Quality System Inspection Technique (QSIT) and medical products risk management using hazard analysis and critical control points (HACCP) Applications. Dr. Aziz earned his MS from Michigan State University, his PhD from American University, and a Post Doctorate in Health Services from the University of Southern California.

SMART DEVICES

Add-On Connectivity Facilitates New Generation of Smart Inhalers

By: Cindy H. Dubin, Contributor, Nemera

INTRODUCTION

The addition of electronic and connectivity to inhalers may improve patient adherence and, consequently, treatment efficacy. This conclusion was unanimously reached by a panel of experts participating in a recent roundtable discussion hosted by Nemera, a France-based designer, developer, and manufacturer of drug delivery devices.

The global connected drug delivery device market is expected to reach $717.7 million by 2025, according to a recent report.[1] Factors contributing to this growth include increased awareness of the adverse effects of non-adherence to medication and increased adoption of connectivity with patient engagement. Analysts claim that leading manufacturers of connected drug delivery devices are collaborating with software companies to assess the feasibility of cloud data system in their devices. No group is more indicative of this trend than inhaler manufacturers, who are racing to develop a new generation of smart devices with sensors to ensure that patients with asthma and chronic lung disease are using their devices properly.[2]

COMMON INHALER MISTAKES

Rescue inhalers that deliver short-acting bronchodilators to relieve sudden respiratory symptoms, and maintenance inhalers that deliver long-acting bronchodilators and corticosteroids to prevent and control respiratory symptoms, are the cornerstone of managing asthma and COPD. Inhalation devices that deliver these medications are available in these basic types:

- Pressurized metered-dose inhalers (pMDIs) consist of an aluminum canister of medication fitted into a plastic body with a mouthpiece. Each dose is delivered by pressing the canister into the plastic body while inhaling through the mouthpiece. Use of a spacer that connects to the MDI removes the need for coordination between inhalation and activation of the device; formulation is first released into the spacer and then inhaled slowly.

- Dry-powder inhalers (DPIs) can be preloaded with the medication(s) inside the device or be loaded by the patient with capsules as the dose-holding system prior to use. A single dose of the medication is loaded and ready to be inhaled, for example, by sliding a lever, twisting a part of the device or, in the case of capsule devices, pressing buttons to pierce the capsule. Patients simply take a deep breath while their lips are sealed around the mouthpiece of the inhaler, and the dose is delivered.

- Soft mist inhalers are a propellant-free liquid inhaler that provides a slow-moving, soft aerosol cloud of medicine to help patients inhale. In comparison with a pMDI, they reduce mouth deposition and generate a "mist of droplets" lasting longer than the pMDI aerosol.

- Nebulizers change medication from a liquid to a cloud of medicine that can last up to 15 minutes. They are used to deliver large doses of drug.

While the correct use of an inhaler depends on the type, at least 70% – and some studies indicate upward of 94% – of patient inhaler users make at least one mistake using their inhaler, resulting in no drug delivered or diminished drug delivered, and potential exacerbation of respiratory symptoms.[2] Mistakes include the following:

"Devices today do not have sufficient capability to provide the patient user with feedback, which is why some mistakes are made." – Raphaële Audibert, Nemera Global Category Manager, Inhalation & Dermal.

- Dose preparation errors – In the case of an MDI, the patient may not shake the canister before each dose or may exhale while actuating the device. In the case of a DPI, the patient may fail to load a dose at all. Or, if a DPI requires piercing a capsule, the patient may not pierce the capsule and may not use a new capsule for each dose.

- Improperly using the device – For example, the patient may fail to remove the cap of the inhaler.

- Improperly holding the device – In some cases, it is not uncommon for the patient to hold the device sideways or at an incorrect angle. If the dose, to be properly loaded or delivered, needs the device to be held in a certain position, it may be incompletely delivered or not delivered at all.

- Inhalation errors – Issues include breath coordination and depth of breath. Patient fails to: exhale fully and away prior to inhalation; inhale slowly and deeply; or hold their breath for a full 5 to 10 seconds.

TYPES OF ELECTRONIC DEVICES

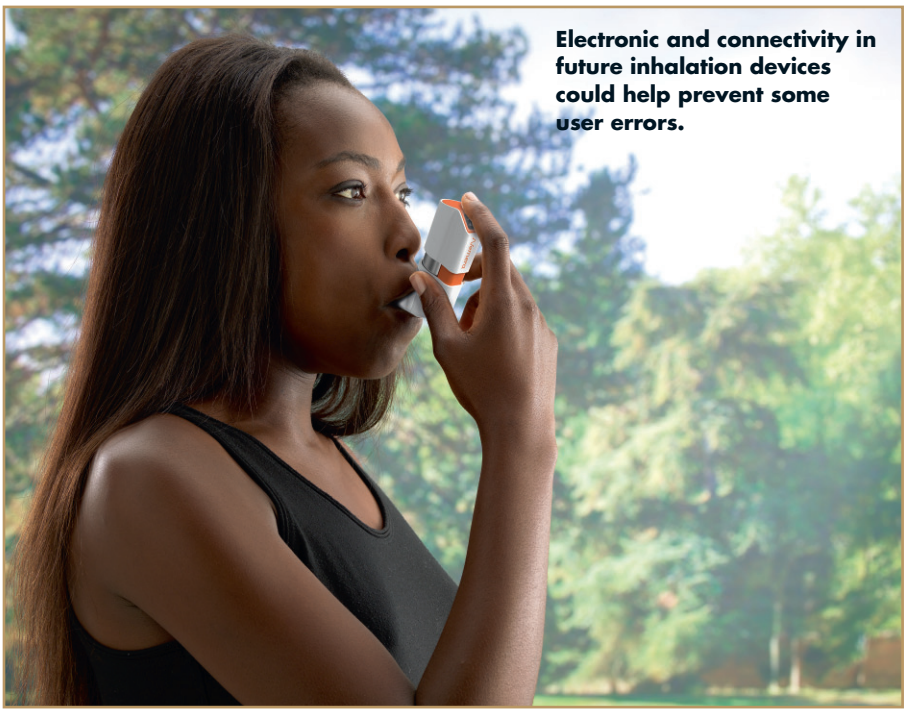
While newer inhalers have design features to remedy these errors, such as dose counters, incorrect use continues to be prominent. "Devices today do not have sufficient capability to provide the patient user with feedback, which is why some mistakes are made," says Nemera's Global Category Manager – Inhalation & Dermal, Raphaële Audibert, who was part of the roundtable discussion. "But, we know that some mistakes can be avoided, and electronic devices are a great way to reduce or eliminate those errors." Electronic devices can be:

- Non-connected devices with different possible features, such as on-device feedback to patient (for example through LED, voice, or screen) or automatic actuation of a device once certain parameters are addressed; and

- Connected devices to enable richer feedback to patients or communication with doctors.

A connected device, such as an inhaler, is connected to a smartphone app or a website to communicate with the patient. This may include sending reminders to take medication and providing usage feedback. This information can also be sent to the patient's doctor to monitor patient adherence and treatment efficacy. Ms. Audibert says the doctor can then determine, in the case of unsuccessful treatment, if it is due to an absence of patient response to a specific drug, if the treatment was not taken as prescribed, or if the patient exhibited poor inhalation techniques, at which point corrective action can be taken.

Electronic drug delivery systems are categorized as either add-ons or integrated devices. Both options have distinct advantages and disadvantages, with both being widespread in development projects throughout the pulmonary spaces. Sensors



Electronic and connectivity in future inhalation devices could help prevent some user errors.

are add-ons that are built around existing mechanical devices and providing tracking and usage information.

"Devices with add-on sensors can record how, when, and where the mechanical activation of a device took place," says Hadrien Gremillet, Strategic Marketing Analyst, Nemera. "These devices will usually provide feedback after administration of the drug, and in some cases, give real-time feedback prior to the administration, such as positioning."

Integrated devices go one step further by enabling, for example, electronic-driven actuation of the device that can be then coordinated with a breath. Adding electronic connectivity requires a printed circuit board (PCB) containing a micro controller and sensors, such as an accelerometer or microcontroller. The integrated device connects to a mobile application or to the cloud via the use of wireless communication elements such as Bluetooth or LTE-M.

CONCEPT DEVICES PROVE CONNECTIVITY IS TRANSFERRABLE

Connectivity is possible with all types of inhalation devices. A few players are already demonstrating their technical capabilities to build such devices. For example, Nemera's knowledge in development, manufacturing, and innovation has resulted in a few concept devices that showcase how electronic features are transferrable across multiple platforms, such as inhalers. One of these concept devices is the e-Novelia®, a smart add-on device for the established Novelia eyedropper.

Electronic features include: tilt sensor and LED indication for device positioning; location tracking; remaining drug indicator; electronic instructions for use (IFU); drop detection; and Bluetooth communication. According to Mr. Gremillet, e-Novelia uses sensors to detect, for example, when the incline of the device is correct, and signals this to the patient via a green light. Digital readouts provide feedback about dosing and remaining medication. And communication with a smartphone app enables medication reminders, and ultimately, patient adherence.

The second concept device from Nemera is e-Advancia®, a reusable, rechargeable add-on device for an established product. Combined with the Advancia® high-performance pump, the add-on features shaking sensors, a display, reminders, dose counter, posology indication, and a connected app.

"For pharmaceutical companies interested in electronic-enhanced devices. we can integrate all our know-how about electronic/connectivity into a specific inhalation project as part of the features obtained are also of interest for inhalation," he says.

THE COSTS OF COMPLIANCE

In a world where hacking exists, users should take steps to secure the connection from the device to the smartphone, from the device to the cloud, the smartphone app, and the cloud itself. Mr. Gremillet says that Nemera has internal experts to provide guidance and support to protect data generated by using electronic devices, which includes specific cloud architectures among other things.

In addition to hacking, device makers are cautious about the price of connectivity. The add-on segment accounted for 72.6% of the connected drug delivery devices market in 2017 and are considered more cost-effective than their integrated counterparts. Moreover, the cost of switching from a conventional system to add-on sensors is relatively low.[1]

Mr. Gremillet says electronics can add costs to the initial mechanical device. However, note that electronic devices are reusable, which spreads the overall cost over many administrations. Additionally, considering the entire treatment path of a patient, electronics can decrease the overall disease cost by limiting costly events, such as hospitalizations. "Device manufacturers, pharma companies, and payers should evolve their business models to consider those decreased hospitalization costs and not just consider the price of the electronics. One cannot quantify improved patient compliance."◆

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BIOGRAPHY

Cindy H. Dubin is an award-winning journalist who has been reporting on the pharmaceutical industry for more than 18 years about a variety of topics, including formulation development, drug delivery, and drug quality.

Special Feature

Excipients: Formulators Want Excipients for Solubility & Beyond

By: Cindy H. Dubin, Contributor

The pharmaceutical excipients market is expected to reach $8.53 billion by 2023, up from $6.4 billion in 2018.[1] Organic chemical excipients had the largest share of the pharma excipients market because of their increased efficacy in oral delivery and increased compressibility and flowability properties. Based on functionality, fillers and diluents dominated the market in 2017 because of their ability to improve taste and ease administration. Additionally, binders experienced growth as they be can co-processed to help overcome formulation obstacles and reduce development costs.[2]

In this annual *Drug Development & Delivery* report, some of the industry's key players discuss the role excipients are playing in continuous manufacturing, biopharma formulation, and controlled- and immediate-release delivery.

Starch 1500® is a partially pregelatinized starch that functions as both a binder and distintegrant, improving coating appearance (Colorcon).

Gattefossé USA: Lipid Excipients Solubilize APIs

Large molecular size, poor aqueous solubility, susceptibility to changes of pH, and enzymatic breakdown are some of the common challenges facing biomolecules today. Such complexities may be addressed by advances in lipid-based formulations or solid dispersions involving polymer-lipid combinations. Otherwise, as poor oral candidates, biomolecules are formulated into injectable forms. Overall, excipients that may improve the dissolution of API and enhance API permeability across the biological membrane are of high interest to drug development scientists.

Lipid excipients fall in the multifunctional excipient category because they fulfill two or more functions in the dose and formulation, explains Jasmine Musakhanian, Scientific and Marketing Director – Pharmaceutical Division, Gattefossé USA. "Polyoxylglycerides like Gattefossé's Geluicre® 48/16 and 44/14 are excellent candidates for low-temperature melt granulation and melt extrusion to obtain granules or multiparticulate systems," she says. "More importantly, they have a biopharmaceutical role to play *in vivo*: Help solubilize the API in the gastric media, trigger fed vs. fasted state environment that is amenable to absorption, and enhance lymphatic transport that is desirable for drugs that are subject to hepatic elimination."

Glyceryl behenate (Compritol®) is a different example among the Gattefossé lipid excipients. Ms. Musakhanian says it helps disperse the drug in a lipid matrix, providing protection against hydrolysis or oxidation for sensitive APIs, and taste masking or sustained-release profile depending on the percentage used.

Dr. Masumi Dave at Gattefossé Technical Center of Excellence, Paramus, NJ.

Evonik Health Care: Solving Solubility is Just the First Step

To achieve bioavailability, many formulators favor the use of amorphous solid dispersions. This will require using polymers as excipients that can form an amorphous embedding, and prevent re-crystallization during storage, says Jessica Mueller-Albers, Strategic Marketing Director, Oral Drug Delivery Solutions, Evonik Health Care. Several polymers in the Evonik EUDRAGIT® portfolio, such as EUDRAGIT L 100-55 and EUDRAGIT L 100, have solid dispersion forming and re-crystallization inhibition characteristics.

However, Ms. Mueller-Albers says that, increasingly, solubility enhancement alone cannot fully address the therapeutic requirements of specialized drugs. That is why many companies are adding controlled-release features to their formulation after the challenge of solubility enhancement has been solved.

In addition to addressing solubility, pharma recognizes that as therapies become more specialized and personalized, excipients must also become more versatile to help streamline the path to market. Advanced functional excipients can reduce formulation complexity, time for QC test-

Evonik's EUDRAGIT® FL 30 D-55 allows highly flexible coatings that remain intact after compression.

ing, and overall regulatory risk, she says. "That is why Evonik has leveraged its new proprietary AEMP™ technology to combine the respective benefits of two existing, monographed polymers to create EUDRAGIT FL 30 D-55. This new combination polymer for enteric coatings enables the design of highly flexible and easy-to-process enteric coatings for dosage forms such as multiparticulate tablets."

EUDRAGIT enteric coatings are also making a valuable contribution in continuous manufacturing. Ms. Mueller-Albers says that pharmaceutical manufacturers should be aware of potential hurdles in continuous manufacturing set-ups caused by some excipients, and that excipient suppliers should have the necessary technical knowledge and robust data sets to validate the suitability of their polymers to be processed continuously. In one recent example, she cites a recent collaboration between Evonik and GEA Process Engineering Ltd to evaluate the performance and design space requirements of EUDRAGIT L 30 D-55 enteric coatings on the Consigma continuous coating module. "Significant increases in manufacturing efficiencies were demonstrated while producing film coatings with excellent quality," she says. "Based on such application data sets, customers will be assured that efficient continuous coating processes can be developed for their products to help shift from batch processing to continuous processing."

BASF Pharma Solutions: Increasing Yield, Mitigating Risk, & Addressing Future Needs

Pharmaceutical formulators are seeking ways to improve the manufacturing process and product quality using multifunctional excipients, which play an important role in innovating delivery technologies and helping in-line extensions of marketed drugs. Moreover, multifunctional excipients can help pharma manufacturing through improved flowability, enhanced compressibility, improved bioavailability, and particle size distribution.

Most of the excipients in BASF's portfolio are multifunctional, meaning that one excipient is suited to meet multiple formulation applications. For example, Kollidon® VA 64 – a copolymer with vinylpyrrolidone and vinyl acetate – is a dry binder for roller compaction and direct compression applications, a film former for coating, and a drug solubilizer in melt extrusion. As a result, Kollidon VA 64 and/or Kollidon VA 64 Fine offer benefits for crystalline, poorly compressible, soluble or insoluble APIs. Other examples include Kollidon SR, a binder and matrix former for sustained-release tablets; and directly compressible excipients, such as lactose-based Ludipress® and mannitol-based Ludiflash®, both of which have been used as dry binders, pore formers for tailoring dissolution profiles, and ready-to-use formulations for tablets and orally disintegrating tablets.

"Excipients are certainly an important consideration when transitioning from batch to continuous manufacturing," says Dr. Krizia Karry, Global Technical Marketing Manager, BASF Pharma Solutions. "They can enable faster process development and a more consistent product performance that ease regulators' concerns about changes to an approved drug product application."

Kollidon® VA 64 is one of many multifunctional excipients from BASF.

Formulators see great promise in multifunctional excipients (Roquette).

Dr. Karry says that raw material properties, such as bulk density, particle size, compressibility, and permeability play an important role in continuous feeding and ultimately the unit formulae of the product. She says that while equipment manufacturers can build controls to mitigate feeder disturbances caused by changes in material properties leading to densification and bridging in hoppers and screws, a complete understanding of the impact of flow properties in process and product performance is essential for continuous manufacturing.

Similarly, adequate selection of raw materials can minimize process and analytical development efforts. "For example, a ready-to-use excipient like Ludipress that has already pre-mixed amounts of binder, filler, and disintegrant can greatly reduce the number of residence time distribution experiments, and simplify efforts in preparing calibration blends for Process Analytical Technology purposes."

Mitigating biological production risks and improving process yield are also important and are driving demand for high-purity excipients. BASF's Kolliphor® P 188 Bio is used to protect cells from shear stress and subsequently increase API yield. "As the industry interest in novel excipients continues to rise due to increase in BCS Class II and IV molecules, BASF is taking a more pragmatic 360-degree approach to address these challenges," says Dr. Karry. "BASF is building partnerships with drug manufacturers, contract research and manufacturing organizations, and equipment manufacturers to develop new polymers using individual monomers as building blocks for unmet formulation challenges." Examples include the PVA-PAA, Soluplus®, and Kollicoat® Smartseal polymers derived from their respective monomer blocks.

Roquette: Multifunctional Excipient Replaces Surfactants

Growth in the pharma industry is a natural driver for the excipients industry, where there is a continuous push to provide functional excipients capable of solving modern formulation challenges. Multifunctional excipients produce a wealth of innovation within the biopharmaceutical industry.

"A current example of this can be seen in Roquette's novel cyclodextrin technology, Kleptose BioPharma," says Peter Ferguson, Roquette's Global Marketing Manager – BioPharma. "This multifunctional excipient provides biopharma formulators with a technology that is well established within small-molecule applications."

Mr. Ferguson explains that the technology is showing great promise in combining different functionalities, such as replacing polysorbates as surfactants while also providing a mechanism for protein stabilization.

"This technology is allowing formulators to respond to market demands, such as managing product lifecycle via a transition from low concentration, powder formulations towards high concentration, liquid dosage forms, administered subcutaneously." New data on multifunctional excipients in biopharma will be released throughout the year from Roquette.

Excipients will also play a crucial role in biosimilar formulations. Mr. Ferguson says while many formulators will look to start their formulation development by using the same excipients contained within the reference product, many will also seek to improve upon the original dosage. This can be seen through the move from intravenous to subcutaneous, from low concentration to high concentration, and from powder to liquid dosage forms. "All of these developments are made possible

through excipient technology and will be a key driver within the biosimilar segment."

Colorcon: Faster & Flexible Coatings

Excipients with consistent quality and physical characteristics play an integral role in continuous manufacturing. For example, excipients with minimal variability can enable longer run times in continuous processes because process adjustments (and potentially stoppages) to offset changing excipient characteristics would not be expected, explains Dr. Ali Rajabi-Siahboomi, Vice President & Chief Scientific Officer, Colorcon. "Innovation in continuous manufacturing is a significant driver of interest in drug delivery technologies and novel formulations."

The end goal of using continuous processes is not necessarily about achieving high-volume throughput, but about adopting lean and consistent manufacturing processes that build quality into the manufacture of the product, rather than testing at the end of the process. "One attribute that the continuous coating process offers, compared to batch processing, is faster and more frequent presentation of tablets to the coating spray zone; this results in shorter cycle times to achieve consistent coating coverage," Dr. Rajabi-Siahboomi says. "Creating an efficient continuous coating process not only depends on the equipment used, but also on the formulation of the coating."

To meet the industry need for faster and more flexible coatings, especially for continuous manufacturing, Colorcon recently introduced Opadry® QX, an immediate-release, quick, and flexible film coating. He says that the coating allows for a higher percentage of solids (up to 35%) and results in a smooth, uniform tablet appearance. "The flexibility of this coating means it can be applied across a range of solids concentrations (20% - 35%), product temperatures, and airflows, making it particularly suited for continuous processing, while the improved coating uniformity inherent in continuous coaters allows manufacturers to take full advantage of improved throughput rates."

Pharmaceutical formulators are also seeking ways to improve the manufacturing process and product quality through the use of functional excipients. Selecting the best excipients, however, requires a balance between time and cost efficiencies as well as anticipated product performance. Multifunctional excipients have traditionally been widely used, often in combination with a range of other excipients. Dr. Rajabi-Siahboomi adds that the overuse of superdisintegrants often creates stability challenges, as well as increasing cost.

Pharmaceutical developers are now focusing on excipients that provide more targeted functionality for a specific manufacturing process. Co-processed excipients offer the possibility of simplifying drug product formulations while meeting functional and technical requirements, he says. "Co-processed excipients are often novel combinations of compendial excipients that offer unique properties and provide formulation and manufacturing simplification."

One Colorcon customer (a large generics manufacturer) recently requested technical support to help reduce the defects observed on a coated tablet. Upon close inspection, the Colorcon technical team noticed that the coating showed discontinuities typically associated with the presence of superdisintegrants in the core. "Occasionally, superdisintegrant particles on the tablet surface can absorb many times their mass in water and disrupt film formation," Dr. Rajabi-Siahboomi explains.

In this case, the customer was encouraged to replace the binder and the superdisintegrant in the core formulation with Starch 1500®, a partially pregelatinized starch that functions as both a binder and distintegrant. Starch 1500 is suited for moisture-sensitive formulations, acting as a moisture scavenger while producing a mix of tablet hardness and rapid disintegration.

"Because Starch 1500 can function as a disintegrant without swelling to nearly the same extent as superdisintegrants, the tablet coating appearance greatly improved and the impact of moisture was eliminated," he says. "The result was a significant improvement in the customer's product appearance while simplifying the overall drug product formulation and reducing the number of excipients used in the manufacturing process. ◆

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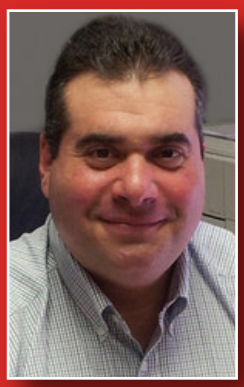

Ed Price
President & CEO
PCI Synthesis

PCI Synthesis: Acquisition by Seqens Expands its Pharmaceutical Offerings

Innovations in science and technology have enabled scientists to create pharmaceuticals, pharma foods, and cosmetics that offer advantages over those existing just a few years ago, as well as therapies to treat formerly untreatable diseases. These require the creation of ever more complex Active Pharmaceutical Ingredients (APIs), a challenge that always begins with the chemistry and can be best met by broadening the expertise a company has available and the opportunities for collaboration. To help meet these challenges, Seqens, a billion-dollar global player in pharmaceutical synthesis and specialty ingredients, acquired US-based CDMO PCI Synthesis. Winner of numerous industry awards, including 24 Life Science Leader CMO Awards, PCI Synthesis is the first US acquisition by Seqens as it expands its geographic scope, complex molecule development range, and its services. Ed Price, President and CEO of PCI Synthesis, is Co-President of the New England CRO/CMO Council and sits on the Board of Governors of the Society of Chemical Manufacturers and Affiliates (SOCMA), the leading US-based trade association representing the specialty chemical industry. *Drug Development & Delivery* recently spoke with him to reflect on the trends fostering the CDMO industry consolidation and the positive impact it augurs in addressing sponsors' needs to enter the clinic more quickly and safely.

"Given the strong US economy with its attendant labor shortages, attracting and keeping talented employees remains a challenge for the industry. Even in pharma and biotech hub Massachusetts, where PCI Synthesis is located and where academic institutions abound, labor shortages are projected. The industry is expected to attempt to fill 11,600 new jobs by 2022, with bio manufacturing jobs seeing a 32% increase over 2016 levels."

Q: What are the major reasons the CDMO sector is seeing greater consolidation?

A: There has been a great deal of growth in the CDMO sector in the past few years as evidenced by our own annual double-digit growth in the past 5 years, which included being ranked on the Inc 5000 list of fastest-growing privately held companies. Several trends are driving this growth. First and foremost, the number of new molecules being developed continues to grow as pharma companies seek to develop new drugs. The major beneficiaries of this trend are US-based CDMOs, for two reasons. First, there is concern about quality issues in India and China that could delay regulatory approval. Second, the industry continues to worry about IP protection, particularly in China.

The value of incorporating Good Manufacturing Practices (GMP) is increasingly being sought by developers of pharma foods too. In contrast to nutraceuticals, which are unregulated, pharma foods include a pharmacological additive that is intended to improve health. Consequently, just like drug candidates, pharma foods undergo clinical testing and must meet FDA guidelines, which is why companies developing pharma foods need GMP. Some expect pharma foods to be the next frontier. We have certainly seen growth in this area.

Demand for medical-grade polymers is also heating up. From novel drug delivery systems to new materials for ophthalmic applications, medical-grade polymers are being used in a range of different applications. We expect demand to continue to grow along with increased use and as new science continues to push the frontiers of what's possible.

Finally, larger companies, such as Seqens, are seeking to fill gaps in their products and services by acquiring US companies that are known to do these things well. Generally speaking, CDMOs with proven track records tend to be of interest to larger players.

Q: What other challenges are driving M&A in the sector?

A: Given the strong US economy with its attendant labor shortages, attracting and keeping talented employees remains a challenge for the industry. Even in pharma and biotech hub Massachusetts, where PCI Synthesis is located and where academic institutions abound, labor shortages are projected. The industry is expected to attempt to fill 11,600 new jobs by 2022, with bio manufacturing jobs seeing a 32% increase over 2016 levels. Despite the fact that Massachusetts and various industry associations are heavily promoting STEM majors, that's not enough to ensure these jobs can be filled. This is another reason M&A is expected to remain strong. In addition to adding products and services, acquisition of smaller CDMOs provides a pool of talented, trained professionals.

On the flip side, for PCI Synthesis, there are also many advantages to consolidation. As business continues to grow, there is a limit to our capacity. This applies not just to manufacturing but also to developing New Chemical Entities (NCEs), supporting projects, and analytical work. These are all

in short supply. Being acquired provides us with the added capacity we need as well as multi-site manufacturing capabilities that ensure a project's timeliness should an unanticipated event occur. For instance, last year's hurricane endangered production of several drugs manufactured in Puerto Rico. The hurricane-ravaged island, whose 80 plants manufacture medical devices and 13 of the world's top-selling and most critical pharmaceuticals to treat cancer, diabetes, and heart disease, was beset by shortage of diesel fuel for the generators needed to keep manufacturing plants running when the electricity went out.

Q: What should drug developers consider in looking for CDMOs now as compared with just a few years ago?

A: As API molecules become ever more complex, pharmaceutical outsourcers should look for a CDMO with very strong technical and analytical capabilities, starting with the R&D operation, which can be evaluated on the basis of these seven key attributes:

1. Low staff turnover
2. Proven ability to innovate and think outside the box
3. Well equipped with a wide array of capabilities
4. Readily available analytic support
5. Scale-up capabilities
6. Technology transfer capabilities
7. Solid track record of meeting regulatory guidelines.

I would stress the need for strong analytical capabilities to avoid regulatory issues that can slow a project down. That can keep a drug candidate from getting into the clinic in a timely fashion and break the budget.

Q: How will access to other Seqens facilities and capabilities provide more benefits to PCI's customers?

A: First and foremost, Seqens has tremendous capacity at their 12 GMP sites, multiple R&D centers, and comprehensive range of services and technologies dedicated to clinical development and commercial manufacturing. Our customers can now easily leverage multi-site, geographically dispersed manufacturing to be closer to certain markets or mitigate the risk of natural or man-made disasters. They will have access to additional technologies, such as high-pressure chemistry, sophisticated solid-state chemistry, and the most advanced GMP manufacturing. They will have the benefit of deep experience in many more types of chemistry that will be useful in more quickly resolving any problems that arise.

Q: How does establishing a larger US presence impact Seqens?

A: The US is the largest pharmaceutical market in the world. Doing business in the US is coveted by many international CDMOs. Although Seqens has facilities in Europe and Asia, many of their customers are in the US. Being located here will bring Seqens into closer proximity to customers, making it easier to communicate to keep projects moving as swiftly as is possible when meeting the challenge of creating new chemistry. Seqens also gains manufacturing facilities in the US, which it does not presently have.

Q: What about PCI Synthesis did Seqens find attractive?

A: Seqens was looking to expand its US business and needed a presence here. But the company was also looking for complementary capabilities. Whereas Seqens projects tend be later stage with customers, PCI Synthesis adds a focus on earlier stage, preclinical projects that are complementary. In addition, we provide infrastructure in the US with medium manufacturing capacity. We also provide a strong brand with our US customer base. Overall, I believe they also saw us as an industry leader in the US in this sector and perhaps even as a model to emulate in managing other internal programs.

Q: What is Seqens's strategy going forward?

A: Seqens is committed to the US, which is why it acquired PCI Synthesis. The combined entity is truly a best-in-class, worldwide CDMO offering to the pharma sector.There is a significant commitment to continue to expand PCI's capabilities and to continue to grow the business by making additional complementary strategic investments in the future.◆

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DRUG DEVELOPMENT

Rapid Preparation of Gadolinium & Protamine Complexes With Aurintricarboxylic Polysalicylates: Implications for Drug Development

By: Timothy J. Smith, RPh, PhD

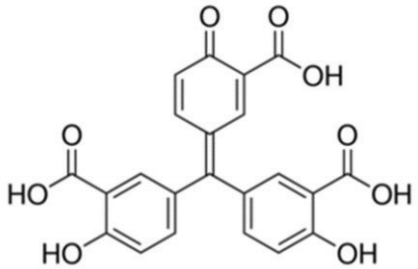
ABSTRACT

Derivatives of aurintricarboxylic acid (ATA), a commercial reagent for aluminum ion determination, are under consideration for drug development in view of ATA's diverse pharmacological spectrum. The ability of this agent to form avid complexes with cations is an important consideration when evaluating ATA and derivatives in drug development, particularly with regard to drug disposition and targeting. Protamine sulfate, an FDA-approved polycationic agent with a wide variety of drug targeting and delivery applications, was used in preparation of a protamine aurintricarboxylate (protamine – ATA) complex. The formation of an insoluble protamine - ATA complex was studied by titration curve analysis, providing evidence that complex formation occurs with most of the polyanionic components of ATA. The ability of this agent to form avid complexes with other trivalent metal ions is an important consideration when evaluating ATA and derivatives in drug development, particularly with regard to drug disposition. The ability of gadolinium (III) complexes to facilitate magnetic resonance imaging could be useful in drug disposition studies of ATA and its derivatives. A gadolinium (III) ATA complex was prepared with gadolinium nitrate hexahydrate and aurintricarboxylic acid (sodium salt). The formation of the insoluble Gd (III) ATA complex was studied by titration curve analysis, providing evidence for stoichiometric formation of the complex with one gadolinium ion to one aurintricarboxylate subunit of ATA. Complexation with protamine and gadolinium (III) may provide interesting approaches to study the disposition of polyanionic ATA and its derivatives.

INTRODUCTION

Aurintricarboxylic acid (ATA), as a commercial preparation, is a mixture of polyanionic components, including the triphenylmethane dye (Figure 1).[1,2] ATA has an unusually wide spectrum of activity; including potential antiviral and antiplatelet applications.[1,2] Although derivatives of ATA may be more suitable candidates for drug development, the polyanionic nature may be retained in many of these derivatives. Counterion complexation of polyanionic ATA may result in a formulation with altered pharmacological targeting and disposition. Among the agents potentially useful for complex formation, the polycation protamine sulfate, approved by the FDA, offers an interesting opportunity to study the disposition and targeting of ATA. Because ATA was originally developed as a reagent for the determination of aluminum ion in various media, the trivalent state of other metals are known to form both soluble and insoluble complexes with aurintricar-

FIGURE 1



Aurintricarboxylic acid subunit.

boxyic acid.[3] Among these trivalent metals is gadolinium (III) or Gd (III), an ion that is used for magnetic resonance imaging (MRI) applications as a chelate.[4] Complexation of ATA with Gd (III) offers an interesting opportunity to study the disposition of ATA and related agents as gadolinium complexes by MRI. This report outlines the preliminary preparation and characterization of the protamine and Gd (III) complexes through rapid titration curve analysis.

COMPLEXATION PROCEDURES

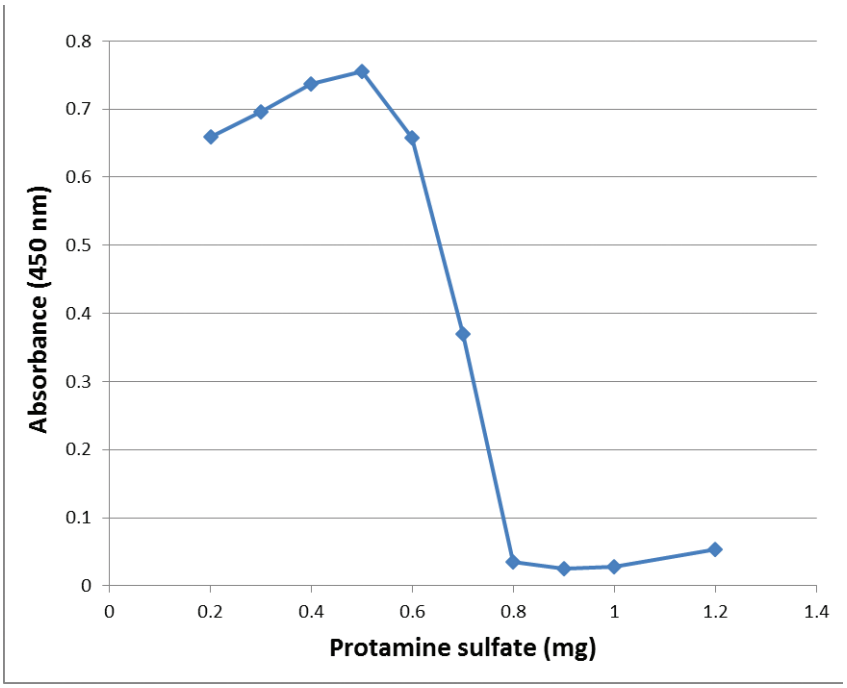
Protamine-ATA

Aurintricarboxylic acid (sodium salt) and protamine sulfate USP were purchased from Sigma-Aldrich (St. Louis, MO). Both agents were prepared in distilled water for complexation. ATA (0.5 mg in 0.25-ml solution) was added to each microcentrifuge tube containing 1 ml of protamine sulfate solution at various concentrations (0.2 mg/ml to 1.2 mg/ml) at 23°C with vortex mixing. To remove the protamine - ATA complex, the microtubes were centrifuged at 2000 x g for 5 mins. The absorbance of the supernatant was read at 450 nm to evaluate the titration of ATA by protamine sulfate.

Gd (III)-ATA

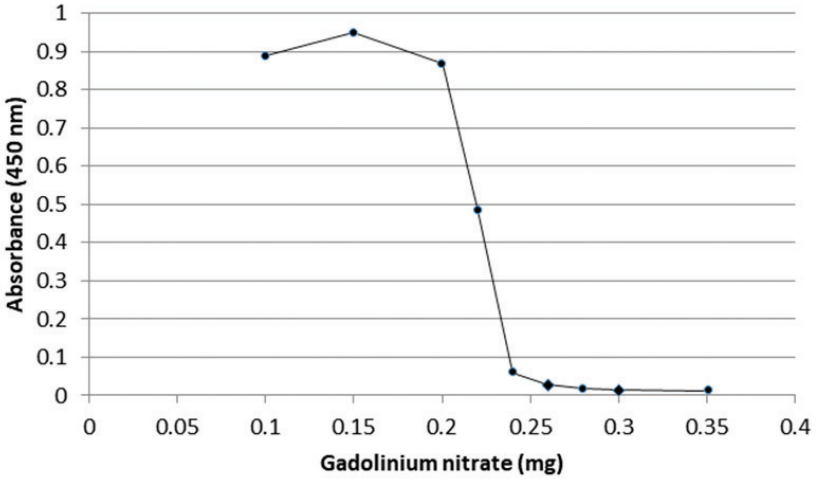
In addition to ATA, Gd (III) nitrate hexahydrate were purchased from Sigma-Aldrich (St. Louis, MO). Both agents were prepared in distilled water for complexation. ATA (0.5 mg in 0.25-ml solution) was added to each microcentrifuge tube containing 1 ml of gadolinium nitrate solution at various concentrations (0.15 mg/ml to 3.5 mg/ml) at 23°C with vortex mixing. To remove the Gd (III) ATA complex, the microtubes were centrifuged at 2000 x g for 5 min. The absorbance of the supernatant was read at 450 nm to evaluate the titration of ATA by Gd (III) ion.

FIGURE 2



Titration curve of ATA with protamine sulfate. ATA (0.5 mg) was added to protamine sulfate in the range indicated, followed by vortex mixing, centrifugation, and spectrophotometric analysis of the supernatant at 450 nm. Points are triplicate determinations.

FIGURE 3



Titration curve of ATA with gadolinium nitrate. ATA (0.5 mg) was added to gadolinium in the range indicated, followed by vortex mixing, centrifugation, and spectrophotometric analysis of the supernatant at 450 nm. Points are triplicate determinations.

RESULTS & DISCUSSION

The formation of the protamine - ATA complex was very rapid and resulted in an insoluble complex, with an increase in ATA absorbance at 450 nm in the presence of protamine (typical of other cations).[5] The results of the titration are shown in Figure 2. The titration curve reveals that the increased presence of protamine results in a slight increase in absorbance during the formation of an insoluble complex. At approximately 1 mg protamine sulfate per ml, complexation is essentially complete, having removed most of the ATA from solution. While the protamine - ATA is somewhat stable under the conditions of this titration experiment, the behavior of the complex in physiological media, both in vivo and in vitro, remains to be determined. Because protamine complexes are relatively stable in vivo and protamine derivatives have applications for cellular delivery of macromolecules, the protamine - ATA complex offers an attractive option to study the disposition and targeting of ATA and its derivatives in future studies.[6]

Likewise, the formation of the Gd (III) ATA complex was very rapid and resulted in an insoluble complex, with an increase ATA absorbance at 450 nm in the presence of gadolinium (as noted previously).[5] The results of the titration are shown in Figure 3. The titration curve reveals that the increased presence of gadolinium results in an increase in absorbance during the formation of an insoluble complex. At approximately 0.3 mg of gadolinium nitrate hexahydrate per ml, complexation is essentially complete, having removed virtually all of the ATA from solution. This point corresponds to approximately 1 ion of gadolinium to each ATA subunit. While the Gd (III) ATA is somewhat stable under the conditions of this titration experiment, the behavior of the complex in physiological media, both in vivo and in vitro, remains to be determined. Since gadolinium chelates are relatively stable in MRI imaging studies, the Gd (III) ATA complex and related complexes are very attractive options to study the disposition of ATA and its derivatives in future studies.[4] ◆

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BIOGRAPHY

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THERAPEUTIC FOCUS

Targeting the Novel LANCL2 Pathway Offers Potential for a Differentiated Treatment Paradigm for Autoimmune Diseases

By: Andrew Leber, PhD, Raquel Hontecillas, PhD, and Josep Bassaganya-Riera, PhD

INTRODUCTION

Landos Biopharma is a clinical stage biopharmaceutical company focused on the discovery and development of first-in-class oral therapeutics for autoimmune diseases targeting the novel lanthionine synthetase c-like 2 (LANCL2). Landos developed a lead clinical asset, BT-11, which affects the pathway by suppressing inflammation and activating regulatory responses in the gastrointestinal tract for treatment of inflammatory bowel disease (IBD). Current IBD therapeutics have mediocre efficacy, poor maintenance of response and damaging side effects, including cancer, infection, and death. There is an unmet clinical need for safer and more effective oral therapeutics for IBD. The new mechanism of action, benign safety profile, and agile management models have accelerated the development of BT-11 and other therapeutics in the Landos pipeline in the path to market.

NEW PATHWAY, DIFFERENTIATED TREATMENT PARADIGM

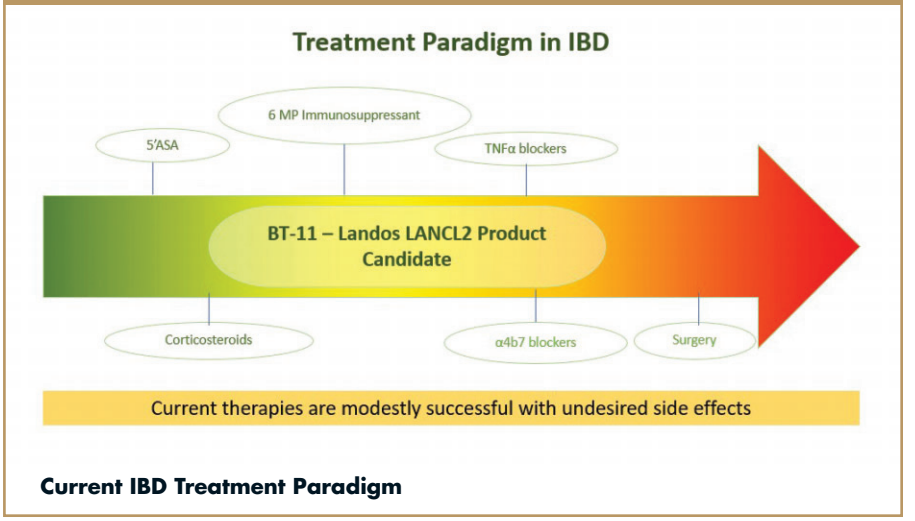
IBD afflicts over 2 million people in North America and 5 million worldwide. Intestinal inflammation - ulcerative colitis (UC) and Crohn's disease (CD) - increases the risk for developing colon cancer, especially at early ages (<30 years).[1] IBD carries a significant burden to patients, often isolating them socially and limiting their professional opportunities.[2] IBD patients have a higher rate of nonparticipation in the labor force.[3] The global IBD therapeutics market, about $10 billion in 2015, according to Global Industry Analysts, is growing 25% annually. Even though current treatments for IBD have improved, they have only modest success in managing chronic disease; many cause significant side effects (eg, infection, cancer, and death).[2,4] This article will focus on the development of BT-11 as a first-in-class, oral, gut-restricted therapeutic for UC and CD.

While BT-11 will be developed as a therapeutic for UC and CD in parallel, we will largely focus description on UC and IBD in general, for the purpose of this article. UC broadly involves defects within both the epithelial barrier and mucosal immune system.[5] In UC, epithelial cells commonly produce lower levels of mucin and form a more permeable barrier layer.[6] These two factors result in greater infiltration of and exposure to intestinal bacteria and other microbes. In response, epithelial and immune cells have increased uptake and recognition of antigens causing a self-perpetuating loop of altered gut microflora, increasing inflammation and damage to the colonic epithelium. Importantly, many genes involved in antigen uptake and recognition, such as major histocompatibility complexes, toll-like receptors, and Nod-like receptors, are common genetic risk factors for UC.[7,8] Immunologically, the balance between inflammatory and anti-inflammatory cell types is skewed in UC patients. This is most apparent within CD4+ T helper (Th) cells, in which Th1, Th2, and Th17 are elevated at the expense of T regulatory (Treg) cells. Specifically in UC, Th2 responses are upregulated increasing production of IL-4 and IL-13, which combine to activate natural

killer T cells.[9] In turn, the NK T cells can attack epithelial and weaken tight junctions. The inflammatory environment is further worsened by increased production of TNFα and chemokines, such as CXCL8, which activate and recruit additional inflammatory cells to the colon.[10] Interestingly, UC patients have decreased levels of Treg cells and reduced levels of serum IL-10 while they have increased levels of serum IL-21.[11]

An important distinguishing factor between UC and other forms of IBD is that UC affects only the mucosal lining of the colon, as opposed to all layers affected in CD. There are four general types of UC ulcerative proctitis, proctosigmoiditis, distal (left-sided) colitis, and pancolitis colitis.[12] Seventy percent of patients who have active disease in a given year will have another episode of active disease in the following year. However, this chronic illness can vary widely over time in severity and disease activity for example, 35% of patients will have one or two yearly relapses, and 11% will remain chronically active for their lifetime. Patients with less severe forms of UC typically undergo 5-animnosalicylic acid (5-ASA) treatment coupled with antibiotics to reduce the general levels of bacteria in the gut and close monitoring of nutrition. Patients that stop responding to 5-ASAs or have a more severe form will take corticosteroids or immunomodulators to suppress the immune system and decrease inflammation. The most severe patients will use biologics such as TNF-α inhibitors as well as surgery when all other medical therapies fail and continuity of the bowel needs to be restored. Treatment failure occurs in approximately 25% of patients receiving aggressive biologics for unknown reasons. Patients with failed biologic treatment plans have only 30% success rate using alternative medications. Moreover, biologics have been associated with increased rates of cancers, infections, and death. Further, the most prevalent treatment, anti-TNFα antibodies with a 68% market dominance, are only effective within 30% of IBD patients.[13] Despite these treatments, an estimated 70% of CD patients and one-third of UC patients still require surgery. Thus, development of innovative IBD oral therapeutics is needed to address this unmet clinical need.

FIGURE 1



Current IBD Treatment Paradigm

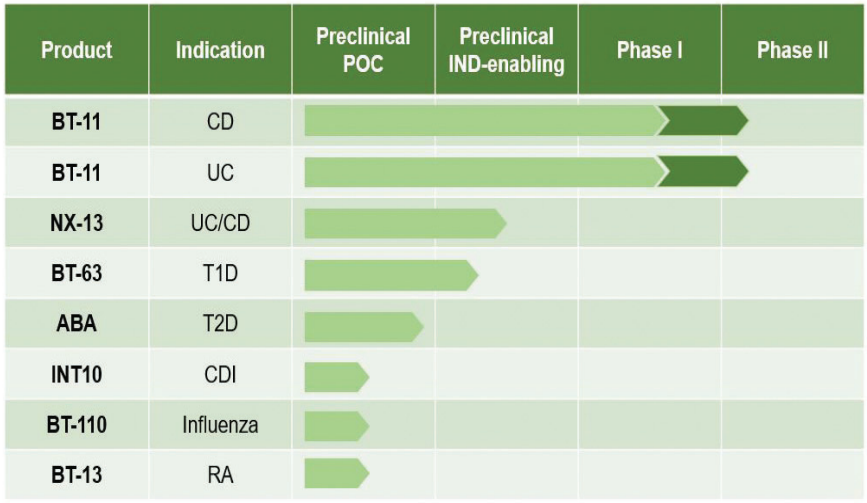
DISCOVERY & DEVELOPMENT

Our discovery work began with the identification of anti-inflammatory and metabolic properties of abscisic acid (ABA), an isoprene phytohormone that is also endogenously produced by mammals. As a naturally occurring phytochemical in fruits and vegetables, dietary consumption of ABA improves glycemic control and can contribute to regulating stress responses. After studying the effects of ABA, we identified LANCL2 as the mammalian receptor for ABA from in silico molecular docking experiments validated with in vitro studies.[14] This systemic activity of ABA, the natural ligand of LANCL2, (included within liver, pancreas, and brain) and its generally recognized as safe (GRAS) classification supported the assertion that LANCL2 is a therapeutic target with a low risk for side effects.[15] Through an extensive pipeline of computational modeling, protein biochemistry, in vivo experiments in animal models, and ex vivo experiments on human cells, LANCL2 was established as a robust drug target for therapeutic development in autoimmune diseases. Based on protein sequence alignment, human and mouse LANCL2 share 88% identity and 94% similarity. Importantly, no amino acid differences are noted within the identified ligand-binding pocket and no shifts in binding pocket structure are predicted, suggesting viable translation of engagement and efficacy from mouse to human. No genetic mutations in the LANCL2 sequence have been associated with a susceptibility to IBD suggesting that LANCL2 is a stable target for pharmacological activation.

We developed a medicinal chemistry program around the LANCL2 target, including a library of over 3 billion novel chemical entities (NCEs) and 48 privileged

scaffolds.[16] The medicinal chemistry enabled optimization of top chemotypes and resulted in the selection of piperazine-1,4-diylbis((6-(1H-benzo[d]imidazo-2-y)pyridin-2-yl)methanone) (BT-11) as the top LANCL2-activating molecule. BT-11 is a piperazine that belongs to a unique chemotype; bis((benzimidazoyl)arylcarbonyl)amides. BT-11 has a lower ClogP (3.93 to 6.78), fewer rotatable bonds (4 to 6), lower MW (528 to 548), greater polar surface area (123 to 116), and smaller total surface area (700 to 719) than other NCEs in that class.[17] After validating the LANCL2 binding affinity and specificity, BT-11 was proven efficacious in five mouse models of IBD spanning chemical injury (DSS), genetic (MDR1a-/-, IL10-/-), bacterial (C. rodentium), and cellular (CD4+ T cell adoptive transfer) models of disease induction.[18] IBD is a multi-factorial human disease that is not easily captured in a single animal model due to its spontaneous onset and flares, complex interactions between the environment, gut microbiome, diet, and genetics and overall patient-to-patient variability. Despite this, the nonclinical evaluation of investigational therapies often relies solely on the use of one or two specialized models. The combination of these five models provides a robust in vivo system to evaluate the therapeutic efficacy of BT-11 in a variety of scenarios involving genetics, immune cells, epithelial cells, and interactions with gut microbiome that enhance confidence of clinical success in Phase 2 and Phase 3 studies.

FIGURE 2



Development Pipeline as of September 2018

MECHANISM OF ACTION & SAFETY PROFILE

LANCL2 activation by BT-11 is a novel therapeutic mechanism in IBD[19] based on four observations — (1) potential to pharmacologically manipulate LANCL2 expression and activation via BT-11, (2) selectivity of BT-11 for LANCL2 as shown by loss-of-function studies in LANCL2 knockout mice and translational siRNA studies in human primary cells from UC/CD patients, (3) potent therapeutic actions of BT-11 in IBD with limited systemic exposure, fast clearance and an excellent safety profile up to 1,000 mg/kg, and (4) high potential for human translation based on PBMC and LPMC data from CD and UC patients.[17-19] Activation of LANCL2 with BT-11 has validated beneficial immunological effects in primary human cells from blood and colonic biopsies of CD and UC donors. LANCL2 expression has been implicated in disease with reduction in expression occurring during periods of inflammation. However, the administration of BT-11 has been identified to rescue suppressed LANCL2 expression. The LANCL2 pathway, validated in five IBD mouse models and human tissues from CD and UC patients, is an innovative MoA, and a therapeutic target for UC and CD.

Through LANCL2 activation, BT-11 has unique immunometabolic mechanisms of action. LANCL2 has a confirmed G-protein coupled signaling pathway with regulation of the signaling molecules PKA, Akt, and mTORC2.[20,21] This pathway results in a net increase of intracellular cAMP leading to activation of the transcription factor CREB which directly modulates cytokine production, a mechanism confirmed to be part of the BT-11 MoA.[17] The resultant upregulation of IL-10 and downregulation of MCP1 and TNFα are cornerstones of BT-11 efficacy in models of IBD. Further, we have recently elucidated effects of BT-11 on late-stage glycolysis of immune cells.[18] The activation of LANCL2 by BT-11 leads to the upregulation of pyruvate dehydrogenase (PDH) activity. With this upregulation, intracellular concentrations of the PDH substrate, phosphoenolpyruvate (PEP), are decreased in mouse and human cells.[18] In addition to its metabolic function as a glycolytic intermediate, PEP is an inhibitor

of SERCA, a regulator of calcium signaling and FOXP3 activity. When either PDH activity or SERCA are inhibited through PS-48 and thapsigargin, respectively, the ability of BT-11 to stimulate FOXP3+ IL10+ CD4+ cellular differentiation is blocked. Importantly, the administration of PS-48 to MDR1a-/- mice abrogates the therapeutic efficacy of BT-11 in mice with IBD.[18] This immunometabolic regulation of FOXP3 allows BT-11 to induce stable populations of Tregs that have enhanced suppressive capacity as evidenced by the decreased proliferation and production of inflammatory cytokines in CD4+ T cells co-cultured with BT-11 treated Tregs.[18] Notable genes integral to the function of Treg cells are increased downstream of FOXP3 in response to BT-11 such as Socs2, Lag3, Helios, and Irf7. These genes allow for the retention of contact-mediated suppression even in inflammatory microenvironments of the GI tract. BT-11 has a multi-faceted mechanism of action with actions on the modulation of immune cell metabolism and favoring regulatory CD4+ T cell phenotypes. The dual nature of BT-11 in actively reducing inflammatory signaling while increasing regulatory signaling is a key competitive advantage compared to anti-TNFα, tofacitinib, anti-integrins and other IBD therapeutics, which soley focus on inhibiting inflammation through a single or small group of molecules.

In addition to potent therapeutic efficacy, BT-11 is a resoundingly safe oral small molecule. PK and bioavailability studies have established that oral administration of BT-11 results in low plasma concentration and systemic distribution with rapid clearance while retaining a high concentration in the GI mucosa (>10,000-fold increases in colonic tissue compared to plasma). BT-11 has been dosed orally in fed and fasted states with no observable differences in plasma concentrations. These profiles indicate the potential for lesser systemic immune effects in combination with high efficacy in reducing inflammation in the GI tract. Indeed, BT-11 has a low potential for side effects and safety concerns. Through IND-enabling studies, BT-11 has a consistent NOAEL >1,000 mg/kg in 3-month GLP-tox studies in rats and dogs and in cardiovascular, respiratory, and central nervous system safety pharmacology studies. BT-11 is non-mutagenic based on Ames, chromosomal aberration, and micronuclei tests. In microsomes and hepatocytes, BT-11 is not metabolized and does not act as a CYP enzyme inhibitor. Additional analysis of urine concentrations supports this claim of a lack of metabolism as similar concentrations of BT-11 are observed in both urine and plasma. While the localization of BT-11 to the GI benefits dosing by allowing a high concentration of therapeutic directly at the site of inflammation, this robust safety data at >100 times the therapeutic dose suggest very low risk of side effects should systemic exposure occur. Additionally, colonic concentrations of BT-11 exceed plasma concentrations by > 10,000-fold. We have examined the route of administration to validate the need for local GI action. In the DSS model, both oral and rectal administration were protective, but IV administration failed to protect from IBD (8 mg/kg) suggesting high GI concentrations are necessary and sufficient to support therapeutic efficacy. The clean safety profile and defined efficacy in non-clinical studies led to the opening of two INDs with the FDA for UC (138071) and CD (128490) in Q2 2018.

CURRENT STATUS & FUTURE DEVELOPMENT

Following the successful filing of two INDs for BT-11, a Phase 1 clinical testing program began in normal healthy volunteers in July of 2018. The study was conducted on 70 male and female volunteers between the ages of 18 to 65 years and weights of 65 to 85 kg. Participants were validated for no clinically significant abnormalities at screening and consented for the study procedures, including administration of BT-11, collection of PK and PD blood samples, ECG, collection and analysis of urine and feces, and routine safety labs. Participants were confined and monitored over the active dosing period and one day after the final dose (2 total days Single Ascending Dose, 8 total days Multiple Ascending Dose). The final report on safety of BT-11, including presentation of adverse events, pharmacokinetic data, and generic safety labs, was available at the end of 2018. The short-term programmatic vision focuses on advancing BT-11 for treatment of IBD along the development pathway toward Phase 2 human clinical trials, followed by Phase 3 studies and a path to New Drug Approval (NDA). Phase 2 studies in UC and CD are on-going in 2019. Landos has built an expansible pipeline of oral therapeutics based on the LANCL2 and other immunoregulatory pathways for Type 1 Diabetes, Rheumatoid Arthritis, Systemic Lupus Erythematous, and Multiple Sclerosis. Given the emergence and global spread of autoimmune diseases, the LANCL2 technology has the potential to significantly impact millions of patients with an unmet clinical need, creating enormous value for the medical/patient community.

AUTHOR'S NOTE

Landos Biopharma's drug candidates described in this article are investigational and undergoing clinical evaluation required by the US FDA for NDA submission. None of the product candidates are approved for commercial distribution in the US or elsewhere.◆

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BIOGRAPHIES

Dr. Andrew Leber is the Scientific Director of Landos Biopharma, where he has led research crossing many disciplines from immunology and inflammation to bioinformatics and computational modeling of immunometabolism. Across all of these disciplines, his work is united under the common theme of identifying novel regulatory pathways and means of activating these pathways for the understanding and treatment of autoimmune and infectious disease. Dr. Leber has contributed significantly to the advancement of BT-11 from preclinical to clinical stage and the expansion of the Landos Biopharma drug development pipeline.

Dr. Raquel Hontecillas is the Chief Scientific Officer of Landos Biopharma. She has 20 years of translational research experience in the biotech industry focusing on infectious, autoimmune, and metabolic diseases. She has identified and validated the role of LANCL2 as a therapeutic target for diabetes and IBD. She managed a $56-million translational R&D program in mucosal immunology centered on the identification of novel immunoregulatory mechanisms during infectious and autoimmune diseases and contributing to the development of novel IBD therapeutics.

Dr. Josep Bassaganya-Riera is the Chairman and Chief Executive Officer of Landos Biopharma. He has 20 years of R&D, business development, fundraising, and entrepreneurial business experience leading biotech companies with innovative, large-scale translational programs in autoimmune and infectious diseases. He has published over 150 peer-reviewed publications, holds numerous patents, has founded three award-winning companies (Landos Biopharma, BioTherapeutics, and Pervida), raising over $78 million in non-dilutive and equity financing rounds, and was recently named 2017 Innovator of the Year. In 2018, he received the Research Excellence Award from Virginia Tech, and Pervida was named Technology Company of the year by the Chamber of Commerce. He is a captain of industry, innovator, serial entrepreneur, and thought leader in biotech. He applies advanced informatics, computational modeling, and systems biology approaches to accelerate the development of innovative technologies into medicines that are safer and more effective.

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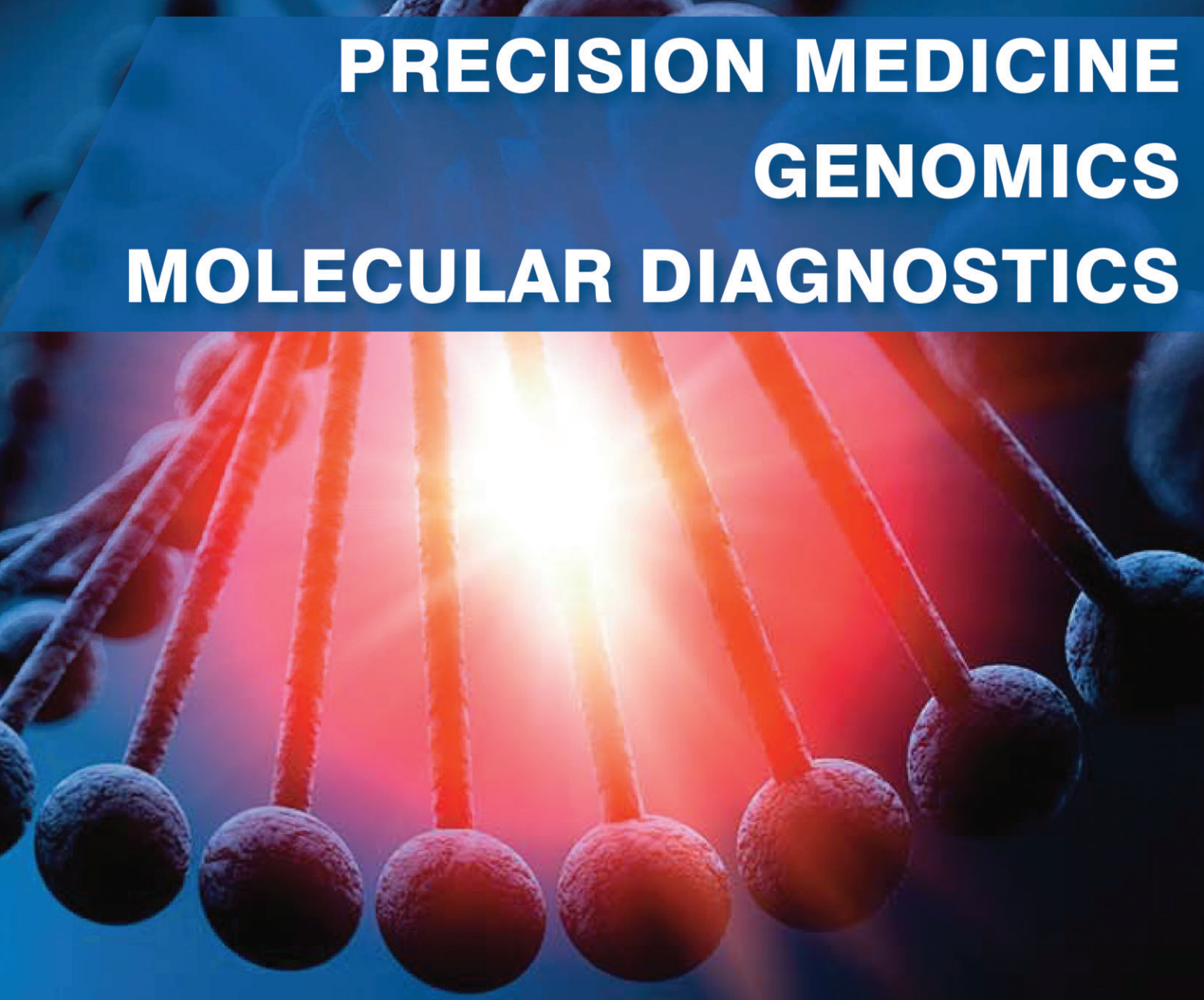

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Which are emerging technologies and growth opportunities for NGS informatics and services?

Technology & Services Showcase

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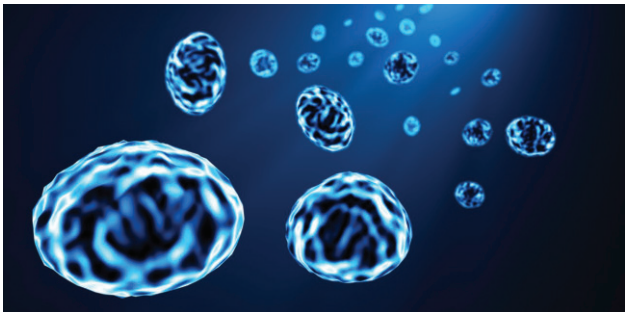

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REAL ESTATE

Four Ways Firms Are Advancing Innovation With Real Estate

By: Roger Humphrey, MBA, BSBA

INTRODUCTION

Life sciences giants across the US are seeking collaborative new ways to reach farther out on the edge of innovation, including by venturing into new frontiers of real estate strategy.

To fuel momentum in the race to fill pharmacy shelves with new therapies, many of the industry's biggest players are teaming up with younger companies and start-ups with which they can leverage new talent and technology. In fact, according to PwC's Health Research Institute, 1 in 3 US biopharmaceutical companies has revamped its approach to R&D, looking to boost productivity by reconfiguring R&D operations and organizational structure, increasing the focus on partnerships.

As companies pursue these collaborative platforms, their real estate needs are changing — with profound implications for how and where life sciences companies choose to operate. Meanwhile, the nation's most desirable markets are exhibiting higher-than-ever costs and lower-than-ever availability, compounding the need for sciences companies to shift priorities and apply their expertise in innovation to formulating new real estate strategies.

Right now, a few strategic shifts are proving most attractive to industry leaders. According to JLL's Life Sciences Outlook report, life sciences firms are pursuing four key areas of innovation in real estate, from expanding dedicated incubator space and following the talent, to pushing outside traditional market boundaries and modernizing laboratory design.

TREND 1: OFFER INCUBATOR SPACE WHERE WILD NEW IDEAS CAN COME TO LIFE

Young companies with great potential can benefit deeply from setting up shop in the nation's top life sciences locations, like Boston, San Francisco, and San Diego. Considering the steep rents in these highly established markets, incubator lab space can fill the gap and bring in these fresh, but relatively under-funded, teams.

So far, the industry is proving keen on this particular trend, with life sciences incubators popping up across the US and becoming a critical part of the R&D ecosystem. Massachusetts, for instance, is already home to more than two dozen incubators.

Part fund, part accelerator, these incubators provide a start-up platform in strategic locations where the key building blocks for life sciences innovation thrive. These spaces nurture the growth of early stage life sciences companies by providing turnkey laboratory and office space, entrepreneurial support, strategic programming, and access to capital. Incubators provide many of the

advantages of being at a big company while providing the flexibility for an entrepreneur to drive scientific research forward.

In some instances, familiar industry names are launching incubator spaces. Alexandria Real Estate Equities, for example, is an urban office real estate investment trust (REIT) that specializes in life sciences and technology facilities. In 2017, the REIT opened the first biotech incubator in New York City with the opening of Alexandria LaunchLabs in Manhattan's East Side Medical Corridor at the Alexandria Center for Life Science.

The Manhattan Alexandria LaunchLabs incubator includes 15,000 square feet of lab and office space that is home to approximately 20 start-up companies. A second Alexandria LaunchLabs will open in late 2018 in Alexandria Center in the heart of Cambridge's Kendall Square neighborhood in Massachusetts.

Alexandria aims to make LaunchLabs a community of small firms, rather than split the lab space up among one or two larger tenants. Companies that join Alexandria LaunchLabs not only gain access to state-of-the-art facilities, but also to strategic risk capital, expertise in early stage company building, and a broad range of advisers.

On the pharmaceutical side, Johnson & Johnson launched its JLABS incubator concept 5 years ago, emphasizing scalability and offering space options ranging from a humble 5-foot bench to a 5,000-square-foot core research lab filled with the latest specialized equipment. Today, JLABS has locations in 11 cities around the world, including its most recent, the 30,000-square-foot JLABS@NYC facility, which opened in mid-2018 in collaboration with the state of New York.

TREND 2: FOLLOW THE TALENT

With increasing innovation and burgeoning new companies, demand for talent is higher than ever before. From scientists and executives to advisers, investors and board members, people are by far the most important ingredient in the life sciences ecosystem.

The life sciences industry continues to be a leading driver of employment across the US, providing 1.73 million jobs at approximately 85,000 companies. In 2017, employers listed almost 264,000 postings for life sciences positions, nearly 10,000 more openings than 5 years ago, according to a study by the Coalition of State Bioscience Institutes.

As a result, finding, attracting, and retaining great people is becoming more difficult in the medical discovery industry, and increasingly critical. According to PwC's Health Research Institute, 51% of biopharma leaders, the highest of any industry, report that hiring has become more difficult and only 28% say they are confident they have access to top talent. And a recent study by MassBio reports that, on average, more than 2.5 months are needed to fill an opening — compared with the 1-month rate that's average across the entire US economy.

The ensuing war for talent is having a ripple effect on major real estate decisions, with life sciences companies intensifying their drive to be near leading academic research centers and the supportive R&D ecosystems that surround them. Case in point: a recent JLL survey of top life sciences companies found that less than 15% of their locations are outside of the top clusters.

What makes the top life sciences clusters distinct is their access to talent. Among JLL clients, nearly 80% of location decisions are based on being close to universities and an R&D ecosystem, despite the high cost of being in the top clusters.

Being in a top life sciences cluster can improve an employer's ability to find and retain life sciences talent as well as access another rising recruitment category: data scientists. The need for tech talent inside life sciences companies will become increasingly important, given the growing use of computing technologies in biopharmaceutical development, from CRISPR gene editing and T-cell therapy to break-

throughs in fields such as computational biology.

TREND 3: EXPANDING THE EDGES OF TRADITIONAL MARKETS

Along with the lack of available talent is a lack of available space. Eight of the top US life sciences clusters as ranked by JLL currently have single-digit direct vacancy rates in their life sciences facilities. How the industry is dealing with exceptionally low availability varies by cluster, and the shortage is driving a variety of real estate solutions across the US. One of the most noteworthy trends is the blurring of the boundaries of the traditional cluster.

A good example is the Innovation Square (iSQ), located in South Boston's Seaport District rather than in Cambridge, but still strategically within the high-tech talent pool that the larger community offers. A phased, 375,000-square-foot R&D life sciences campus, iSQ is the first multitenant lab facility to be developed in this part of the city, but momentum is already hot. The first two floors of the phase I building will be occupied by anchor tenant Mass Innovation Labs, an accelerated commercialization program that is also launching new sites in Brighton and Cambridge.

Another example of new projects in new locations is TMC3, a 1.5 million-square-foot collaborative research campus that will break ground in 2019 at the Texas Medical Center (TMC) in Houston — generating even more interest in this breakout cluster. The new biomedical research hub will bring together researchers and industry experts from across the public and private sector throughout its collaborative 30-acre campus. The centerpiece of the TMC3 campus — designed to resemble the double helix shape of a DNA strand — will be a multistory facility that houses shared core labs, retail, and commercial space.

Outside of the top clusters, new life sciences collaborations are sprouting up in premier locations for medical care, research, and education to accelerate innovation. Consider, for example, the new incubator in Orlando, FL's Medical City, which is the center of the University of Central Florida's Health Sciences Campus and now home to the region's first life sciences incubator.

Through the incubator program, entrepreneurs gain access to the area's facilities, plus resources for research and coaching. These kinds of schemes could help bring R&D firms closer to their end users — patients — and also help contribute to the kind of environment that will attract more talent.

TREND 4: NEW LABORATORY DESIGNS FOR A NEW GENERATION OF TALENT

The decline of the blockbuster drug has forced a reckoning in laboratory design — one that's exposed new pathways to a more agile, future-friendly lab. The dark labs of yesteryear are giving way to lab designs that incorporate natural light, sustainability features and attractive sight lines that, ideally, will promote well-being and inspire creative thinking about research problems.

Historically, reconfiguring a pharmaceutical or biotech lab to support research for an all-new remedy or cure has been a time-consuming and expensive undertaking. But that's changing as life sciences companies increasingly steer clear of conventional lab design in favor of smaller, flexible spaces to keep up with the pace of innovation. Now, many industry giants are redesigning for flexibility and collaboration to become nimbler and accelerate research and product development.

They're also leveraging new occupancy planning technology to ensure enough space to remain productive and engaging, while avoiding a glut of underutilized space. According to a JLL survey of top life sciences companies, space utilization has been increasing in the latest lab projects, with lab-space-per-scientist reduced by 25% in new Class A facilities, compared to older labs.

These tighter footprints for labs help facilitate creative interaction with colleagues, preferably without requiring degowning, and can be easily reconfigured to accommodate different kinds of research to help scientists perform their studies as quickly as possible.

In addition, mobile benches and unassigned workspaces are being used to allow for fast changes in personnel and/or the type of work being performed. Some lab designers are installing retractable electrical cords in the ceiling and technical infrastructure into moveable facades so workspaces can be set up in different configurations around the lab floor, rather than being limited to fixed walls. Another strategy is to build in heavy-duty floor slabs in laboratory corridors to accommodate periodic moves of heavy equipment.

Finally, as a result of the growing promise of computational science, traditional labs are shrinking to make way for more office space. In terms of lab design, the evolution represents a fairly significant shift in space utilization. More traditional

R&D facilities typically were split between 75% lab space and 25% computational space. New designs are gravitating toward 50% lab and 50% computational space.

INVESTMENT IN INNOVATION: MORE THAN A PASSING PHASE

The war for talent, soaring patient populations, vast industry promise, and competitive pressure. These market conditions are here to stay, at least for the foreseeable future. But even as industry giants and incubators tackle these challenges in a more collaborative R&D environment, where research can potentially spawn many different drugs, other forces are also converging to drive innovation.

INVESTORS ARE KEEN ON INDUSTRY INNOVATION

Funding trends indicate that momentum is likely to last. Venture capital investment in life sciences companies surpassed $11 billion in 2017, and 2018 is on track to set a new record, although most of this is still centered in the top clusters.

Investing in early stage biotechs is providing the resources to nurture drug development and is bringing drugs to market faster and cheaper. But, while early stage start-ups are fueled with more funding than ever, investors are skipping early seed funding and investing more following the actual clinical proof of concept. As a result, the sector has added a number of new unicorns: private companies with billion-dollar valuations.

The implication of this changing dynamic is that today's early stage biotech start-ups have more resources than their peers 5 years ago. This should enable better clinical programs, more expansive pipelines, and, combined with the rise in access to real estate resources through platforms, such as incubators and accelerators, enhanced innovation to bring more drugs to market faster and cheaper.

The year 2018 ended with a flurry of initial public offerings (IPOs) based on a backlog of well-financed private biotechs with premium valuations. With nearly 40 biotechs and pharmas going public nationwide in 2017, up from 29 in 2016, the IPO market looks healthy.

BIOPHARMA INDUSTRY LEADERS ARE RAMPING UP R&D SPENDING

Fueled by a desire for innovation and new medical breakthroughs, biopharma companies were among the top companies in 2017 to post an overall increase in R&D spending. While tech companies spent more on R&D than any other sector in the S&P 500, top biopharma companies weren't far behind.

The uptick in R&D spending is one more factor that points toward a strong future of innovation for the industry, including significant advances in biological sciences and pharmaceuticals, and the expansion of more effective drugs and curative and preventive treatments aimed at enhancing the quality of human life.

The US life sciences innovation ecosystem is vibrant. Building on collaborative research at teaching hospitals, universities, and research institutions, innovation now progresses through start-ups funded by venture capital and into established biotech and pharmaceutical companies funded by the public markets. And while each component of the ecosystem plays a distinct role, they can all be connected in physical space, often for the better.

The aforementioned trends explored illuminate the ways in which real estate is becoming more than a backdrop of labor, but a vital platform for innovation. By investing in the right locations and facilities today, a company can position its operations for long-term agility and further advance the ultimate goal of R&D: the next great breakthrough. ◆

To view this issue and all back issues online, please visit www.drug-dev.com.

BIOGRAPHY

Roger Humphrey is the Executive Managing Director, Industries, and Leader of JLL's Life Sciences Group, guiding a team of more than 3,000 professionals dedicated to developing customized solutions for the entire real estate and facilities management lifecycle. His team is accountable for providing facilities management, transaction management, lease administration, design/construction/project management, and portfolio management to leading life sciences firms. He came to JLL from Merck & Co., Inc. where he built and staffed the Global Real Estate Services department, which provided portfolio strategy, occupancy planning, workplace innovation, and transaction management for a 100-million-square-foot portfolio that spanned 750 sites in 80 countries. He earned his MBA from Babson College and a BSBA with a concentration in Finance from Northeastern University.

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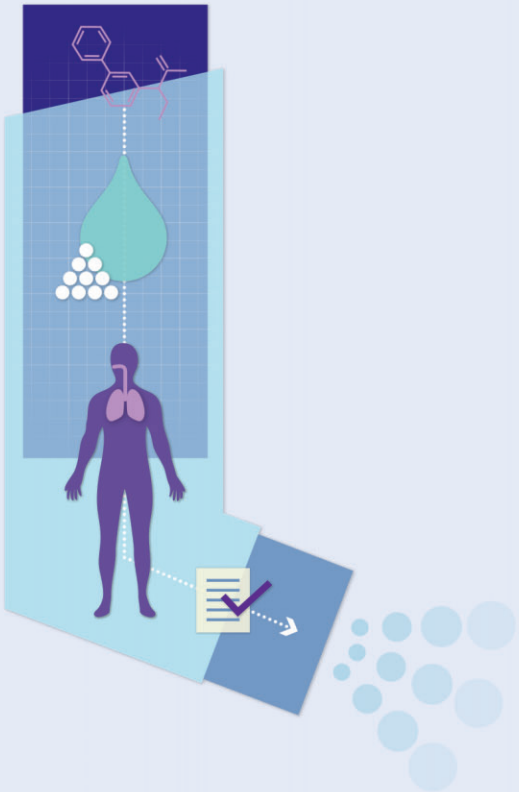

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