Improving Bioavailability & Solubility

Cindy Dubin
Improving Bioavailability & Solubility: Chemical & Physical Modification vs. Formulation Development

Travis Mickle, PhD
Prodrugs for ADHD Treatments: Opportunities & Potential to Fill Unmet Medical Needs

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When it comes to delivering drug product, you need a CMO with longstanding commercial expertise to ensure fast time to market.
“Sufficient drug solubility behavior remains one of the most challenging aspects in formulation development. Adding to this challenge is that there are even greater time demands being placed on drug development as the market becomes even more competitive. Some developers point to chemical and physical modifications for improving bioavailability/solubility while others claim formulation and delivery methods are effective.”

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“What’s needed is a renaissance in drug delivery and formulation technology development, the type that was seen four decades ago and lasted for the better part of thirty years. Drug delivery has had its greatest impact when it has identified whole new product ideas and delivered the necessary technologies. But this renaissance will require new ideas and the resources, financial and technical, to be realized.”
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Nitric oxide (NO) is a crucially important molecule proven to play a critical role in a broad array of biological functions. Inhaled nitric oxide is currently approved for treating term and near-term neonates with Persistent Pulmonary Hypertension of the Newborn (PPHN) in the US and most major markets. In Europe, Japan, and Australia, inhaled NO is approved to treat PPHN as well as pulmonary hypertension during the peri-operative cardiac surgery period in neonates, children, and adults. In the airways, NO is believed to play a key role in the innate immune system at concentrations ranging from 1 part per million (ppm) to 80 ppm. It is a significant advantage in the hospital setting by greatly reducing inventory and storage requirements and improving overall safety with the elimination of NO2 purging steps, among other benefits.

 Persistent pulmonary hypertension of the newborn (PPHN) is a life-threatening condition secondary to failure of normal circulatory transition at birth. It is a syndrome characterized by elevated pulmonary vascular resistance (PVR) that causes labile hypoxemia due to decreased pulmonary blood flow and right-to-left shunting of blood. Its incidence has been reported as 1.9 per 1000 live births (0.4–6.8/1000 live births) with mortality rate ranging between 4%-33%. This syndrome complicates the course of about 10% of infants with respiratory failure and remains a source of considerable morbidity and mortality. NO gas is a pulmonary vasodilator and is approved in dozens of countries to improve oxygenation and reduce the need for extracorporeal membrane oxygenation (ECMO) in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilator support and other appropriate agents.

AIT’s ventilator-compatible NO Generator and Delivery System is a cylinder-free, phasic flow nitric oxide delivery system and has been designated as a medical device by the US FDA. The device can generate NO on demand for delivery to the lungs at concentrations ranging from 1 part per million (ppm) to 80 ppm. The elimination of the need for large, high-pressure cylinders for NO is a significant advantage in the hospital setting by greatly reducing inventory and storage requirements and improving overall safety with the elimination of NO2 purging steps, among other benefits.

Mogrify Raises $3.7 Million to Accelerate Mission to Transform Cell Therapy Via Direct Cellular Conversion

Cell Mogrify Ltd (Mogrify) recently announced a second close on its seed funding, bringing the total raised to $3.7 million, and the appointment of Darrin M. Disley, PhD, DSc, OBE, as CEO. The company will use the funding to market novel IP and cell types generated using its proprietary direct cellular conversion platform, which will power the development and manufacture of life-saving cell therapies across all therapeutic areas. The funding round was led by existing investor Ahren Innovation Capital (Ahren), with 24Haymarket and Dr. Disley also investing.

Mogrify builds on a 10-year investment by its co-founders in the development of a systematic big data-science approach (Rackham et al., Nature Genetics, 2016) powered by next-generation sequencing and gene-regulatory data to identify the optimal combination of transcription factors (in vitro) or small molecules (in vivo), needed to convert any mature cell type into any other mature cell type without going through a pluripotent stem cell- or even a progenitor cell-state.

The company is applying this approach to address the issues of efficacy, safety and scalability currently associated with cell therapy development and manufacturing, which is estimated to represent a $30-billion market opportunity and is rapidly growing (CAGR +30%). Further, through its internal development and partnership programs, the company is positioned to directly address growing markets that are unserved by approved cell therapies, such as cardiac repair and cartilage regeneration end-user markets, estimated to be worth $120 billion and $7 billion by 2022 and 2025, respectively.

Mogrify’s leadership team is of significant commercial and scientific caliber. The Company was founded by leading academics in bioinformatics, Professor Julian Gough (LMB, Cambridge, UK), cell reprogramming, Professor Jose Polo (Monash University, Melbourne, AU), and machine learning, Assistant Professor Owen Rackham (Duke-NUS, Singapore), and is chaired by Professor Steve Jackson, FRS, Ahren Science Partner, originator of Olaparib/Lynparza, and University of Cambridge Professor of Biology.

Dr. Disley is a renowned scientist, entrepreneur, angel investor, and enterprise champion who has started, grown, or invested in over 40 start-up life science, technology and social enterprises, raising $500 million in business financing and closing $600 million in commercial deals. He was CEO of Horizon Discovery Group plc for 11 years, during which he led the company from start-up through a $113-million IPO, and rapid scale-up powered by multiple acquisitions of US peer companies to become a global market leader in gene editing and gene modulation technologies. He was appointed OBE in 2018 for his services to business and enterprise in the healthcare sector.
Genocea Announces Private Placement Financing of Up to $39 Million

Genocea Biosciences, Inc. recently announced it has entered into a private placement with certain existing and new investors providing for the purchase of up to approximately $39.2 million of its common stock and warrants to purchase shares of Genocea common stock, in two closings.

In the first closing, Genocea will offer 25.6 million shares of common stock and 4.25 million pre-funded warrants to purchase common stock, along with accompanying warrants to purchase 0.25 shares of common stock for each share of common stock or pre-funded warrant purchased by an investor, for expected aggregate gross proceeds to Genocea of approximately $15 million (before deducting fees to the placement agents and other offering expenses payable by Genocea).

The warrants will be exercisable immediately upon issuance, in whole or in part, at an exercise price of $0.5656 per share and will have a 5-year term. The first closing of the private placement is expected to occur on or about February 14, 2019, subject to customary closing conditions.

Contingent on satisfactory top-line immunogenicity results from the ongoing Phase 1/2a clinical trial for GEN-009, Genocea’s neoantigen vaccine candidate, expected in late second quarter or early third quarter of this year, Genocea will have the option to conduct a second closing and sell up to an additional $24.2 million of shares of common stock to the investors who participated in the first closing at a purchase price per share equal to the greater of $0.4713 per share and a per share price that is derived from the volume weighted average price of the common stock for the period between the public release of the Phase 1/2a data and Genocea’s exercise of its option to proceed with the second closing. An investor in the first closing that does not purchase at least 50% of the shares that it specified it would purchase in the second closing will forfeit any unexercised warrant purchased in the first closing.

Genocea intends to use the net proceeds from the offering to support the ongoing clinical study of GEN-009, advancing GEN-011, a neoantigen adoptive T cell therapy candidate for the treatment of cancer, toward an Investigational New Drug Application with the U.S. Food and Drug Administration, and for working capital and other general corporate purposes.

Genocea’s mission is to help conquer cancer by designing and delivering targeted cancer vaccines and immunotherapies. While traditional immunotherapy discovery methods have largely used predictive methods to propose T cell targets, or antigens, Genocea has developed ATLAS, its proprietary technology platform, to identify clinically relevant antigens of T cells based on actual human immune responses. Genocea is currently studying the safety, immunogenicity, and efficacy of its lead neoantigen cancer vaccine, GEN-009, in a Phase 1/2a clinical trial.
Evotec & Galapagos Enter Global Collaboration

Evotec AG and Galapagos NV recently announced a global collaboration focused on a novel target for fibrosis and other indications. The collaboration concerns a small molecule program, currently in preclinical drug development for the treatment of fibrotic diseases of the liver and other organs. The target has been identified and validated using Evotec’s proprietary platforms for fibrotic diseases and NASH. Evotec utilized its in-house assay development and drug screening capabilities to identify small-molecule modulators against the target, which remains undisclosed.

In exchange for global commercialization rights to Galapagos, Evotec receives an upfront payment, and is eligible for potential milestone and royalty payments. Galapagos will be responsible for all further development of the program. Furthermore, Galapagos will have access to specific screening formats at Evotec to support the final preclinical development.

Dr. Cord Dohrmann, Chief Scientific Officer of Evotec, said, “We are delighted to be working with Galapagos on this innovative project in an area of high unmet medical need. The team at Galapagos share our focus on novel, first-in-class therapeutic candidates and we are glad to be part of their portfolio building.”

“Following the Fibrocor partnership announced early January, the collaboration with Evotec recently announced again underlines our commitment to expanding our fibrosis franchise,” added Dr. Piet Wigerinck, Chief Scientific Officer of Galapagos. “We highly regard the scientific know-how of Evotec, and are hence very much looking forward to collaborating with the team.”

Evotec is a drug discovery alliance and development partnership company focused on rapidly progressing innovative product approaches with leading pharmaceutical and biotechnology companies, academics, patient advocacy groups, and venture capitalists. We operate worldwide, and our more than 2,500 employees provide the highest quality stand-alone and integrated drug discovery and development solutions. We cover all activities from target-to-clinic to meet the industry’s need for innovation and efficiency in drug discovery and development (EVT Execute). The company has established a unique position by assembling top-class scientific experts and integrating state-of-the-art technologies as well as substantial experience and expertise in key therapeutic areas including neuronal diseases, diabetes and complications of diabetes, pain and inflammation, oncology, infectious diseases, respiratory diseases, and fibrosis. On this basis, Evotec has built a broad and deep pipeline of approx. 100 co-owned product opportunities at clinical, pre-clinical and discovery stages (EVT Innovate). Evotec has established multiple long-term alliances with partners including Bayer, Boehringer Ingelheim, Celgene, CHDI, Novartis, Novo Nordisk, Pfizer, Sanofi, Takeda, UCB and others.

Galapagos discovers and develops small molecule medicines with novel modes of action, three of which show promising patient results and are currently in late-stage development in multiple diseases. Our pipeline comprises Phase 3 through to discovery programs in inflammation, fibrosis, osteoarthritis, and other indications. Our ambition is to become a leading global biopharmaceutical company focused on the discovery, development, and commercialization of innovative medicines.
BrainStorm Announces First Contracted US Clinical Site for Phase 2 Progressive MS Study

BrainStorm Cell Therapeutics Inc. recently announced Cleveland Clinic as the first US clinical site contracted for a planned Phase 2 open-label, multicenter study of repeated intrathecal administration of autologous MSC-NTF cells in participants with progressive Multiple Sclerosis (MS). The Phase 2 study (NCT03799718) will enroll progressive MS patients [Expanded Disability Status Scale (EDSS) 3.0-6.5] based on 2017 revised McDonald Criteria.

MS is a chronic neuroinflammatory and neurodegenerative disorder that affects the brain and spinal cord. MS affects approximately 1 million individuals in the US and 2.5 million individuals worldwide. Approximately half of affected individuals will eventually develop a progressive disease, which may lead to increasing levels of motor, visual, and cognitive functional impairment and disability.

“We are very excited to announce The Mellen Center for MS Treatment and Research at Cleveland Clinic as the first contracted US clinical site for this very important Phase 2 progressive MS study that we plan to initiate in early 2019,” said Chaim Lebovits, President and CEO of BrainStorm. “This is a crucial step forward toward rapidly enrolling a Phase 2 study to evaluate this innovative autologous cell therapy approach using our NurOwn technology platform in progressive MS patients.”

“Progressive MS treatment options are limited and do not directly address unmet need,” said Ralph Kern, MD MHSc, COO, and CMO of BrainStorm, “This phase 2 clinical trial is an important part of our commitment to bring a new treatment modality and hope to MS patients.”

Cleveland Clinic is currently ranked as the No. 2 hospital in the country, according to U.S. News & World Report (2017-2018). The Mellen Center for Multiple Sclerosis Treatment and Research at Cleveland Clinic is one of the largest and most comprehensive programs for MS care and clinical research worldwide, managing over 8,000 patients and over 21,000 total visits annually.

NurOwn (autologous MSC-NTF) cells represent a promising investigational therapeutic approach to targeting disease pathways important in neurodegenerative disorders. MSC-NTF cells are produced from autologous, bone marrow-derived mesenchymal stem cells (MSCs) that have been expanded and differentiated ex vivo. MSCs are converted into MSC-NTF cells by growing them under patented conditions that induce the cells to secrete high levels of neurotrophic factors. Autologous MSC-NTF cells can effectively deliver multiple NTFs and immunomodulatory cytokines directly to the site of damage to elicit a desired biological effect and ultimately slow or stabilize disease progression. BrainStorm is currently conducting a Phase 3 pivotal trial of autologous MSC-NTF cells for the treatment of amyotrophic lateral sclerosis (ALS). BrainStorm also recently received U.S. FDA acceptance to initiate a Phase 2 open-label multicenter trial in progressive MS and plans to start enrollment in early 2019.

BrainStorm Cell Therapeutics Inc. is a leading developer of innovative autologous adult stem cell therapeutics for debilitating neurodegenerative diseases. The company holds the rights to clinical development and commercialization of the NurOwn technology platform used to produce autologous MSC-NTF cells through an exclusive, worldwide licensing agreement. Autologous MSC-NTF cells have received Orphan Drug status designation from the US FDA and the European Medicines Agency (EMA) in ALS.
Formulation Research Strategy for Discovery-Stage New Drug Candidates

By: Jim Huang, PhD, Founder & CEO, and Edward Orton, PhD, SVP, Ascendia Pharmaceuticals

“I believe things cannot make themselves impossible” – Stephen Hawking

Drug discovery medicinal chemistry programs typically involve generations of multiple lead compounds, which must be evaluated according to various selection criteria, such as:

- Selectivity of binding to target site
- Efficacy in animal disease models
- Adequate bioavailability for selected route of administration
- Adequate half-life and biodistribution
- Satisfactory exploratory toxicity in vivo
- Chemically stable and able to be synthesized at scale

The selection process allows a drug candidate along with one or more backup candidates to be chosen for preclinical development from a set of lead compounds. Thus, in vivo studies of new drug candidates at this early stage take on great importance. Negative or ambiguous results may well lead to erroneous conclusions regarding candidate advancement. In worst case scenarios, research programs may be terminated based on flawed data.

Discovery-stage formulations have intrinsic limitations (eg, limited quantities of drug candidates), and these couple with the exigencies of discovery research to introduce risks such as:

- Purity of drug substances may not be optimal
- Key physicochemical properties (eg, log P, pKa) of compounds are typically not experimentally determined
- Solid state properties (eg, crystallinity, polymorphism) are unknown
- Availability of drug substance limits number and precision of solubility measurements that can be performed
- Stability of drug substance in formulations is typically not fully evaluated
- Rapidly developed HPLC assays (eg, non-validated gradient methods) contribute some degree of inaccuracy in solubility measurements and may not give reliable indication of drug stability

Despite these limitations, formulation scientists can provide early stage formulations that manage risks, enable clear inferences from the results of in vivo studies, and allow differentiation between multiple leads. The holy grail of discovery formulation is identifying a "universal formulation" for a structurally similar lead series. This simplifies differentiation of in vivo behavior amongst several leads.

Throughout the past decade, large pharma companies have cultivated pharmaceutical scientist teams to conduct formulation researches for early stage compounds. During this same period, there has been a rapid growth of academic institutes, biotechs,
and other types of start-up companies entering the drug discovery arena. However, access to discovery formulation specialists is restricted within the realm of large pharma. Even though many CROs specializing in pharmacology studies do offer formulation services, these are typically standardized concoctions that produce poorly characterized formulations and may include excipients (DMA, NMP, etc) that might not be acceptable for in vivo use in some animal models.

Therefore, it becomes critically important that CROs or CDMOs that support discovery and preclinical research have the requisite preformulation, formulation, and biopharmaceutics expertise as well as the proprietary methodologies to develop formulations from small quantities of drug candidates for different routes of administration (PO, IV, IN, IM, SC etc). An ideal approach to drug development involves a thorough understanding of the physical-chemical and biopharmaceutical properties in relationship to drug dissolution, absorption, and the disposition process in the body while taking advantage of advanced formulation technologies. A rational formulation design can be explored with guidance from a decision tree (Figure 1).

Discovery-stage formulation scientists approach drug solubilization first from consideration of the molecular structure and calculated log P and pKa values in combination with any experimental data (solubilities, melting point, etc) provided. Micro-scale solubility screening using co-solvents, surfactants, lipids, and complexing agents (cyclodextrins) will indicate what formulation approaches will be feasible. Particle size reduction can also be a viable approach for crystalline lead compounds. Small-volume media mills can produce nanocrystal suspensions with volumes of less than milliliters.

Often, multiple formulation approaches will be combined. Judicious choice of formulation excipients can improve solubility for a candidate by several orders of magnitude. Thus, a drug candidate may be transformed from 1 µg/ml intrinsic solubility to 100 µg/ml with concomitant improvement of the PK profile. These early studies will often yield important experimental results that will aid subsequent development of clinically relevant dosage forms. The key outcomes from early stage formulation studies should support the emerging target product profile. Further, valuable intellectual property may develop when non-obvious biopharmaceutics effects are discovered during formulation development. This can enhance the new drug entities’ patent portfolio beyond the basic composition of matter filings.

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Maintaining the structural integrity of a biotherapeutic, up to the point of delivery, is essential to safeguard its safety and efficacy. During the biomanufacturing process, there is potential for proteins such as monoclonal antibodies (mAbs) to undergo conformational changes, which alter their secondary structure, leading to critical variations in functionality. The characterization of mAbs at high concentration (150 mg/mL), in clinically representative formulations, without the need for dilution, or concern for interference from a formulation buffer’s excipient, is therefore vital. Such analysis helps scientists to understand and control the impact of processing conditions on the structure of the drug product. On the other hand, earlier stages of drug development call for analysis at much lower concentrations in far simpler samples. The most common limitation of traditional analytical techniques for the characterization of protein structure is that they operate across a narrow concentration range, but an ability to robustly characterize structure in the presence of excipients can also be an issue.

Biotherapeutics are typically delivered intravenously or subcutaneously in liquid formulations, often at relatively high concentrations to minimize administration time within the limitation of having a stable formulation of practical viscosity. Sample dilution complicates measurement as well as introducing an additional source of analytical variability, and the extrapolation of measured results to higher concentrations is widely recognized as a potential source of error in biopharmaceutical characterization because of the sensitivity of protein structure to its surrounding environment.

FTIR, although recognized for 50+ years as a powerful technique, is inherently disadvantaged for protein characterization due to its lack of dynamic range, weak optical source, and lack of automation.
limiting referencing techniques. Ultraviolet-circular dichroism (UV-CD), in contrast, is an established tool for structural analysis at more dilute concentrations (typically operating in the range 0.2 to 2.0 mg/mL) but is unsuitable for direct measurement at high formulation concentrations and formulations containing interfering excipients.

We worked with Celldex to test Microfluidic Modulation Spectroscopy (MMS), against their conventional analytical tools for mAbs analyses. MMS is a protein characterization technique that combines a microfluidic flow cell and a tunable mid-IR quantum cascade laser source to assess the stability, similarity, quantitation linearity, denaturation, and aggregation of proteins by analyzing the absorbance spectra and determining the higher order structures (HOS).

MMS uses a tunable mid-IR quantum cascade laser to generate an optical signal hundreds of times brighter than the conventional sources used in FTIR spectroscopy. Brighter sources also allow the use of simpler detectors without the need for liquid nitrogen cooling. Additionally, the sample (protein) solution and a matching buffer reference stream are automatically introduced into a microfluidic flow cell, and the two fluids are rapidly modulated (eg, 1 to 4 Hz) across the laser beam path to produce nearly drift-free background compensated measurements.

To evaluate the data quality and performance of MMS versus conventional mid-IR and far-UV -CD techniques, a mAb formulated at relatively high concentration, with a RedShiftBio AQS3™pro MMS instrument at different concentrations from 1 mg/mL to 150 mg/mL.

The data shows that the differential absorbance spectra (diffAU) replicates for each sample are very closely matched, indicating high repeatability and accuracy of the MMS measurements. The maximum diffAU signal versus protein concentration data fits a straight line with an R² value of 0.999, displaying exemplary quantitation linearity across the concentration range, from 1 mg/mL to 150 mg/mL. The absolute absorbance spectra (absAU) of the antibody samples at concentrations from 1 mg/mL to 150 mg/mL overlay very well, suggesting a common secondary structure profile of these samples. When comparing the Area of Overlap (AO) plots to the mean AO plot of the sample replicates, the similarity is greater than 98% across the entire concentration range.

A detailed HOS analysis yields consistent secondary structure estimations for these samples, ie, 59%-61% beta sheet structure, 28%-29% turn structure, and very small amounts of alpha-helix and unordered structures. No dilution of high concentration samples is required for MMS measurements, and there are no interferences from optically active components in formulation buffers. The results clearly demonstrate that MMS delivers accurate, highly reproducible protein characterization across a dynamic range far broader than can be accessed via conventional IR and CD techniques. Furthermore, they highlight the strength of MMS as a powerful technique for the characterization of HOS and comparability studies involving complex protein samples formulated with excipients.

Dynamic range is one of the biggest challenges we hear from formulation scientists when characterizing proteins with current techniques. Celldex and others have highlighted that a key advantage of MMS is its wide dynamic range. MMS can measure over many decades of concentration, from 0.1 to 200 mg/mL (down to 0.01 mg/mL for protein quantification applications), in contrast to the single decade of concentration measurement associated with alternative techniques for measurement of the secondary structure of proteins, such as FTIR and UV-CD. The ability to consistently measure at the concentration of interest from the early stages of biopharmaceutical development through formulation into manufacture, with a single technique, with negligible requirements for sample dilution/concentration, is a major gain.

Future Characterization Corners columns will address challenges faced during the biophysical characterization of proteins.

Thank you to Ioannis A. Papayannopoulos and Shannon Renn-Bingham at Celldex Therapeutics, 151 Martine Street, Fall River, MA, 02723, for providing the data.

## FIGURE 1

<table>
<thead>
<tr>
<th>Sample concentration</th>
<th>Similarity (%) of replicates</th>
<th>Mean±SD</th>
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<tbody>
<tr>
<td>1 mg/mL</td>
<td>98.74</td>
<td>98.22</td>
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<tr>
<td>*5 mg/mL</td>
<td>99.84</td>
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<td>10 mg/mL</td>
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<tr>
<td>150 mg/mL</td>
<td>99.18</td>
<td>99.18</td>
</tr>
</tbody>
</table>

*The similarity data was obtained by comparing the Area of Overlap (AO) to the mean AO of 5 mg/mL replicates.
RNA EDITING

New Editing Technology Enables Body to Repair its Own RNA

By: Daniel A. de Boer

INTRODUCTION

An in-house novel RNA-editing technology called Axiomer® may be the treatment answer for people with rare genetic conditions. Axiomer utilizes a person’s own RNA repair mechanism. It can be used to attract this mechanism to a specific mutation in the RNA, where it alters a single nucleotide to repair the mutation and restore the broken or missing protein. Around 20,000 disease-causing mutations have been identified that can be reversed with Axiomer technology, which has many specific advantages it offers relative to DNA-editing techniques.

ADARS, THE KEY TO AXIOMER TECHNOLOGY

The key to Axiomer technology is a class of endogenous enzymes called adenosine deaminases acting on double-stranded RNA (ADARs). ADARs are responsible for binding to double stranded RNA (dsRNA) and are responsible for converting adenosine (A) to inosine (I) through a process called deamination. The net effect of A-to-I editing at the RNA level is effectively an A-to-G change in the original DNA code. There are two ADARs that have been identified, ADAR1 and ADAR2. Both have been shown to be expressed in most human tissues. These ADARs exist for two known purposes: as a defense strategy against RNA-based viruses and as a means of site-specific gene editing via A-to-I substitutions.¹

All known ADARs share a highly conserved catalytic deaminase domain. They are responsible for the conversion of adenosine to inosine and a variable number of double-stranded RNA-binding domains (dsRBDs). It’s the dsRBDs that are the key to the Axiomer technology: ProQR’s scientists realized that it would be possible to utilize these regions to make targeted corrections to disease-causing mutations at the RNA-level. Through the design of specialized editing oligonucleotides (EONs), short single-stranded RNA molecules with a sequence complementary to a known mutation, ProQR can recruit endogenous ADARs to the mutation site to make a needed A-to-I substitution (Figure 1). We have also been developing computational EON design approaches that help achieve high-potency for making RNA corrections. These corrections, while targeted and initiated by synthetic EONs, are completed by a person’s own repair machinery, which essentially helps people repair their own RNA.

FIGURE 1

Axiomer® EON-Directed Therapeutic Editing

COMPUTATIONAL DESIGN APPROACHES HELP PREDICT & OPTIMIZE EONS FOR AXIOMER

Because EONs are the key to Axiomer technology, rational EON design strategies are necessary to ensure the creation of effective RNA-editing therapies. This could help streamline a poten-
RNA molecules are naturally less stable than DNA due to the presence of a hydroxyl group attached to the 2’ position of the sugar-phosphate backbone, making the molecules more prone to degradation. Our team realized that by making 2’ modifications to an RNA-based EON, it is possible to increase its stability, resulting in a longer-lasting RNA-editing effect. Increasing EON stability also has the effect of requiring a lower dose for effective editing as well as increasing the duration of effect before additional administrations of the treatment are required to prolong the therapeutic effect.

Rational EON design relies both on computational and empirical approaches to achieve high potency and drug-like properties. To guide the process of optimal EON design, scientists used the ADAR2 structure as a template and calculated atomic models of the protein bound to an EON-RNA complex. This allowed researchers to generate a map of specific positions within the EONs, while bound to their RNA target, that do not tolerate 2’ modifications because of their propensity to alter the interaction with ADAR. Following this predictive computer modeling, we can screen and verify these EON oligos with in vitro experiments. Through successive validation of the computer-generated model, the process of designing novel EONs for therapeutic purposes is now greatly streamlined. This unique design can make modifications to EONs that improve the efficiency of RNA editing.

VALIDATING AXIOMER TECHNOLOGY WITH A HURLER SYNDROME MOUSE MODEL

One of the most common mutations that causes Hurler syndrome in humans, IDUA W402X, results from a single DNA base change (TGG -> TAG). This simple mutation causes protein transcription to end prematurely, resulting in a shortened and non-functional iduronidase enzyme. An analogous mutation, IDUA W392X, causes Hurler syndrome in mice. Because this is a similar G-to-A mutation, it can be used as a test model for Axiomer’s A-to-I editing in RNA (inosine is the RNA equivalent to guanine, ‘G’, in DNA). As a first in vivo proof-of-concept test of the potential for Axiomer technology to be used as a novel therapy for genetic disorders, we designed and screened a panel of EONs targeting this mutation. Testing the EONs showed that the technology had the ability to restore full-length iduronidase mRNA expression (Figure 2a). In addition, IDUA W392X targeting EONs also restored iduronidase enzyme activity in the mouse model system (Figure 2b). It also caused a decrease in the accumulation of GAGs suggesting that Axiomer therapy was working as predicted (Figure 2c).

BROAD POTENTIAL FOR THERAPEUTIC A-TO-I EDITING

Being able to alter the course of Hurler syndrome in a mouse model is just
the first step of many for this technology. The goal is to create transformative therapies so that patients and families will not have to suffer from debilitating rare genetic conditions. With Axiomer technology, this technique can potentially be brought to bear on a wide variety of conditions. There are currently over 23,000 G-to-A mutations known to result in a genetic disorder and, with Axiomer, all these sites potentially become targets for therapeutic intervention.

Not all G-to-A mutations cause a complete loss of function on a protein. One example is Hurler syndrome, in which the mutation directly leads to a shorter non-functional product. Sometimes the DNA base substitution leads to a change in a single amino acid of a protein. Changing an amino acid can alter the function of a protein without changing its level of expression. This can lead to protein malfunction, where the protein is still expressed at the right levels and in the correct cells. Simply lacking the ability to function properly can also cause disorders. Additionally, some G-to-A mutations will occur in sections of the genome that are not responsible for directly encoding a functional protein. Instead, these mutations will occur in a region responsible for controlling gene expression. This results in a significant increase or decrease in the amount of certain proteins, which can also be the cause of health problems. These are all additional instances where Axiomer’s rationally designed EONs can potentially intervene and restore altered gene expression caused by genetic mutation.

Axiomer technology offers several advantages over other existing gene-editing techniques currently being applied to the treatment of genetic disorders, such as CRISPR/CAS9 and traditional viral-based gene therapy. First, EONs are small molecules that do not require a vector for delivery. Accurate and efficient payload delivery is a major challenge for many gene-editing techniques due to the large size of the required molecular components (for example, CAS9 enzymes can run anywhere from about 3 kB to 5 kB in size, more than 100x the size of EONs). The small size of EONs required for targeted RNA editing in Axiomer in combination with the fact that the repair enzyme, ADAR, already exists in almost all human target organs. This is the basis for a simpler gene-editing system overall.

In addition, CRISPR genome editing creates permanent changes to a person’s genetic code. Many viral vectors that are being used for gene therapy integrate their viral genomes into the host’s DNA. This alters the genome in a permanent fashion. Permanent alterations of the genome, when solely therapeutic, can be positive. But recent evidence has surfaced demonstrating off-target CRISPR editing that suggests there are significant inherent risks to using this technique. Off-target genome editing can disrupt other normally functioning genes and can cause health problems or toxicity of their own. EONs used for Axiomer have high-fidelity for their intended target such that there is a low probability of off-target activity. In addition to the non-permanent nature of Axiomer, any potential damage that could happen to the RNA will not be permanent.

SUMMARY

Axiomer technology, a powerful RNA-editing technique that enables the body to repair itself, is being developed as a next-generation therapeutic option for genetic disorders. With the potential to make a difference in thousands of conditions, Axiomer is primed to be a major part of the current revolution in personalized targeted therapeutics.

REFERENCES


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BIOGRAPHY

Daniel A. de Boer is a Dutch serial entrepreneur and the founding Chief Executive Officer of ProQR Therapeutics since the company’s incorporation in 2012. When his newborn son was diagnosed with a rare genetic disease, he decided to start ProQR to develop drugs for rare genetic diseases. Prior to founding ProQR, he was the founder and CEO of several IT companies, including RNA Systems, PC Basic, and Running IT, which he led through several phases of growth. Mr. de Boer is also co-founder and advisor to the CEO at Amylon Therapeutics.
Our Capabilities Have Grown Broader But Our Focus Is As Clear As Ever.

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PRODRUG TECHNOLOGY

Prodrugs for ADHD Treatments: Opportunities & Potential to Fill Unmet Medical Needs

By: Travis Mickle, PhD

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurological disorder associated with an ongoing pattern of inattention, hyperactivity, and/or impulsivity that may impede, for example, cognitive and social functioning, and as well as mental growth and development. Since 1937, more than 25 different products have been approved by the FDA to treat ADHD. Despite the many pharmacological advances, there is still no optimal treatment of this condition, leading prescribers and patients to press for improvements that address key shortcomings with currently available ADHD medications. Duration of efficacy, consistency of drug exposure and effect, onset of action, and lower abuse potential are just some of the key attributes that new technologies are seeking to address.

In the quest for the optimal ADHD medication, leading researchers and drug developers have utilized prodrug technologies to potentially fill this treatment gap. Prodrug technology has been successfully utilized to develop therapeutics and to treat patients for more than 100 years. Many of the world’s best known and most widely used pharmaceuticals are prodrugs, with aspirin being a prime example.

Elegant in concept, prodrugs are inactive, bioreversible derivatives of an active parent drug molecule that must undergo an enzymatic or chemical transformation after administration in a patient in order to release the parent drug, which can then elicit its desired pharmacological effect. To improve therapeutic effect, a prodrug may enhance the physicochemical, pharmacological, and/or pharmacokinetic properties of its parent drug. Key properties that prodrugs can potentially modify generally fall within one or more of the ADME categories — Absorption, Distribution, Metabolism, and Excretion — with the goal being the creation of a new chemical entity (NCE) that optimizes the performance, utility, and potential life-cycle management of the parent drug.

ADHD THERAPEUTIC MARKET

The Centers for Disease Control and Prevention noted in a 2016 report from the National Survey of Children’s Health that 6.1 million, or 9.4% of children aged 4 to 17, suffer from ADHD. Yet, of all children 2 to 17 years of age that may qualify to take ADHD medication, only about 317,000 (or 1 in 20) are currently being treated. Globally, there are a reported 175 million cases of ADHD in people 5 to 44 years old, and the forecast indicates that this number will rise to more than 185 million by 2025.

There are two active ingredients that physicians predominantly select for ADHD therapy, both of which belong to the class of stimulants. These two stimulant medications are 1) methylphenidate-based products like Ritalin, Methylin, Concerta, Focalin XR, and the Daytrana Patch, and 2) dextroamphetamine-based products like Adderall, Adderall XR, and Vyvanse. Methylphenidate is generally prescribed as the preferred first-line therapy for children under 13 years of age, whereas older patients are more commonly treated with dextroamphetamine.

In addition, there are non-stimulant treatments that have been approved by the FDA, such as atomoxetine (Strattera®), clonidine (Kapvay®), and guanfacine (Intuniv®). Published findings report that the use of non-stimulants may reduce the risk of certain side effects like agitation, sleeplessness, or lack of appetite. However,
doctors usually prescribe these medicines only after first-line treatments fail to produce the desired result.

Not surprisingly, not all patients respond equally to ADHD treatment or even to the same active ingredient. Prescribers need to consider several aspects of the therapy and the state of the patient’s disorder. These considerations include, but are not limited to, the speed with which the medication enters the brain and how the patient responds when the medication is delivered. For example, short-acting formulations release the active immediately but only last for a few hours, necessitating multiple daily doses in most patients. On the other hand, longer-acting products are formulated to provide sustained plasma concentrations throughout the day and therefore may only require once-daily dosing. Different treatments may have different side effects, which may prompt doctors to test multiple medications to find the best therapy for each individual patient.

Another concern in treating patients with stimulants is the potential “rebound effect” that may occur when the medication wears off, resulting in the return of ADHD symptoms temporarily, sometimes in an amplified form. In children, this often triggers increased irritability and/or aggressive behavior. The rebound may be more pronounced when high levels of synaptic dopamine decrease quickly as a result of a short-acting stimulant being rapidly cleared from the system. This may be exacerbated by multiple short-acting drug administrations used sometimes to obtain the desired duration of therapy.

Finding the right dose that is effective and minimizes unwanted side effects is among the biggest challenges in ADHD treatment. What works for one patient may not work for another. Identifying the optimal therapeutic regimen that is just right is a process that can be challenging for parents, patients, and prescribers.

THE PRODRUG OPPORTUNITY

Prodrug technology may provide at least a partial answer to addressing key patient/prescriber needs that remain unmet with the current ADHD medical regimes, namely onset of action, duration, consistency of drug delivery for a more predictable therapeutic effect, and abuse potential. Some evidence of this potential can be found in today’s market-leading ADHD medication, Vyvanse®, which is a prodrug of d-amphetamine.

Developed by New River Pharmaceuticals and approved by the US FDA for patients 6 to 12 years of age in 2007 and for adults in 2008, Vyvanse was designed as a prodrug of d-amphetamine for the treatment of ADHD. Though products marketed at the time, such as Adderall® and Concerta®, were determined to be safe and effective in treating the symptoms of ADHD, there was a recognition within the medical community that those products were suboptimal for certain patients.

Vyvanse was developed as a prodrug (lisdexamfetamine), a treatment form that differed from formulation approaches by utilizing the body’s own enzymes to convert the therapeutically inactive prodrug molecule to the active parent drug, d-amphetamine. In clinical studies, Vyvanse was shown to be efficacious throughout the day (up to 13 hours) in both children and adults (up to 14 hours) with once-daily dosing, addressing a key unmet need in ADHD therapy. Additionally, as shown in animal models, the prodrug is not readily converted to d-amphetamine when administered through non-oral routes of administration that may be used to abuse these products (e.g., injecting, snorting), a property which has been viewed as beneficial by physicians aware of the abuse potential of stimulant medications. Other benefits include low inter-patient and intra-patient pharmacokinetic variability. In addition,
“Even though Vyvanse represented an advancement for amphetamine-based ADHD therapies, a decade later, clinicians and ADHD patients still desire new and innovative therapies that offer earlier onset and longer duration of effect than the current methylphenidate products are able to provide. Specialty pharmaceutical company KemPharm, Inc. is seeking to potentially meet this need by developing two novel ADHD products that utilize a prodrug of methylphenidate.”

because these properties of Vyvanse are not imparted by its formulation, patients can sprinkle the prodrug on food or dissolve it in a liquid for ingestion, thereby providing a benefit to pediatric patients or those that may have difficulty in swallowing.

Ultimately, and perhaps due to Vyvanse’s unique product attributes, New River Pharmaceuticals and its Vyvanse product were acquired by Shire for $2.6 billion in 2007. Today, Vyvanse is the branded market share leader in ADHD treatment with reported 2017 sales topping $3.2 billion.

Even though Vyvanse represented an advancement for amphetamine-based ADHD therapies, a decade later, clinicians and ADHD patients still desire new and innovative therapies that offer earlier onset and longer duration of effect than the current methylphenidate products are able to provide. Specialty pharmaceutical development company, KemPharm, Inc., is seeking to potentially meet this need by developing two novel ADHD prodrug candidates intended for the treatment of ADHD that utilize a prodrug of methylphenidate.

**TAKING ADHD PRODRUGS TO NEW HEIGHTS**

KemPharm, which was founded in 2006, has a strategy that is focused on discovering and developing prodrugs that are new molecules and can improve one or more attributes of approved drugs, such as the duration of action, bioavailability, and susceptibility to abuse. KemPharm’s ADHD prodrug portfolio, highlighted by its two lead product candidates, KP415 and KP484, exemplifies this strategy and the potential advantages that prodrugs may offer in meeting patient/prescriber needs across the ADHD spectrum.

KP415 is an investigational ADHD product candidate containing a prodrug of d-methylphenidate, serdexmethylphenidate (SDX), with extended-duration properties, co-formulated with immediate-release d-methylphenidate. Its design is intended to address unmet needs with currently marketed methylphenidate ADHD treatments, such as onset of action (eg, 30 minutes), duration of efficacy (eg, 13 hours), and consistency of the therapeutic effect. In addition, the prodrug component of KP415 may offer the possibility of lower abuse potential due to its unique metabolism.

KP484 utilizes the same prodrug, SDX, but with a different formulation. The objective is to develop a “super-extended duration” d-methylphenidate product (up to 16 hours of efficacy), positioning KP484 for the treatment of ADHD in patients that respond best when a very long duration of therapy is required. Typically, this patient profile aligns with the adult ADHD market. It is estimated that 10.5 million adults have ADHD, making adult patients the largest segment of the ADHD market.

Clinical data for KP415 and KP484 have thus far supported the design goals of both prodrug products. KemPharm recently reported top line results from a classroom-style efficacy and safety trial of KP415, which met pre-specified primary and secondary endpoints in patients with ADHD between the ages of 6 and 12 years. KP415 produced statistically significant improvements in multiple endpoints, such as inattention, hyperactivity, and impulsivity, with generally well tolerated adverse events consistent with stimulant therapy. While an FDA review will ultimately determine the approved duration of action, the totality of data from this study suggests that KP415 has the potential to address the
market need for a therapy with early onset of action and extended duration of effect.

As the FDA has required a human abuse potential assessment in order to determine the drug schedule for SDX, the abuse-related effects of the prodrug are being evaluated in several ongoing and recently completed trials. In one of these studies, an intravenous (IV) human abuse potential study, SDX demonstrated a statistically significant reduction in maximal (Emax) Drug Liking (primary endpoint) when compared to d-MPH hydrochloride, and no statistical difference versus placebo. Emax of Take Drug Again was statistically lower for SDX compared to d-MPH hydrochloride. Additional secondary endpoints including Emax of Overall Drug Liking, Feeling High, and Good Effects were also significantly reduced for SDX compared to d-MPH hydrochloride, but were similar for SDX and placebo.

Clinical studies of KP484 have also shown promise, with data suggesting that the prodrug product may produce a longer duration release of d-MPH compared to currently available MPH products. Importantly, because KP484 utilizes the same prodrug as KP415, a large portion of the data from current and ongoing KP415 studies, including nonclinical toxicology, clinical pharmacokinetics, and human abuse potential studies, may also support the KP484 program, allowing for an expedited development pathway.

SUMMARY

Due to the fact that ADHD can manifest itself differently in each patient, it can be a complicated condition to treat. While current ADHD medications generally work well, there are still unmet medical needs requiring new therapeutic approaches. A prodrug treatment offers the potential to meet several of these unmet needs.

For now, KemPharm is leading the way in prodrug ADHD treatment development as it continues to explore clinical studies in both children and adults. Improved onset of action, longer treatment duration, and possibly reduced abuse potential are a few of the value potentials that prodrugs are capable of delivering in the ADHD marketplace. Moreover, prodrug solutions for other medical conditions also hold promise across the entire pharmaceutical spectrum.

Author’s Note: the views expressed herein are those of the author and do not necessarily reflect those of other entities mentioned.

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Dr. Travis Mickle is the President, CEO, Chairman of the Board, and Co-Founder of KemPharm. The company was founded in 2006 with the discovery of its LAT™ (Ligand Activated Therapy) prodrug platform. Dr. Mickle oversees KemPharm’s business and scientific strategy and is instrumental in the ongoing development of the company’s pipeline of proprietary prodrugs. Prior to founding KemPharm, he served as Director of Drug Discovery and CMC at New River Pharmaceuticals, where he was the principal inventor of Vyvanse®, a prodrug of amphetamine for the treatment of attention deficit hyperactivity disorder (ADHD). Dr. Mickle has been granted over 40 US patents, over 20 EP (Europe) patents, and has authored more than 100 patent applications US and worldwide, focused on prodrug therapies for pain, ADHD and CNS disorders, including multiple patents for prodrugs of hydrocodone, methylphenidate and amphetamine. He is also the principal or secondary investigator on several published abstracts and publications. Dr. Mickle earned his PhD from the University of Iowa, and his BA from Simpson College.
TRANFORMATIONS IN NEXT-GENERATION SEQUENCING

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Which are emerging technologies and growth opportunities for NGS informatics and services?
Sufficient drug solubility behavior remains one of the most challenging aspects in formulation development. Adding to this challenge is that there are even greater time demands being placed on drug development as the market becomes even more competitive. Some developers point to chemical and physical modifications for improving bioavailability/solubility while others claim formulation and delivery methods are effective.

“Physical and chemical modifications allow for thermodynamic stability of the system, allowing for not only maximum shelf life, but also practical dosage forms like tablets and capsules,” says Dr. Frank Romanski, Global Technical Marketing Manager, BASF Pharma Solutions.

“The chance to improve solubility of a drug by chemical modification is usually limited to the very early stages of development,” counters Dr. Jessica Mueller-Albers, Strategic Marketing Director for Oral Drug Delivery Solutions at Evonik. “Chemical modifications, such as varying the salt being used, may also change your pharmacokinetics and pharmacodynamics. That is why there are few instances where this method alone has been successfully applied to improve drug solubility.”

As a result, there have been innovations in formulation development that create a variety of options to enhance solubility and optimize physiological absorption. “Since there won’t be any impact on the pharmacological behavior of the drug, this pathway provides more freedom and a higher probability of success,” says Dr. Mueller-Albers. Physical modifications and formulation are closely related to each other, and can have a significant impact in retaining bioavailability over time. Because this interplay will have a de-
cissive role for all downstreaming processes, it is the key to attaining drug product sta-

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In this annual Drug Development & Deliver
EmulSol, and NanoSol,” says Jim Huang, PhD, CEO, Ascendia Pharmaceuticals. “These advanced approaches allow us to meet stringent timelines and solve difficult challenges with compounds. Offering three technologies allows Ascendia Pharma to address these compounds more efficiently, especially those with the most challenging chemical properties.”

Ascendia also utilizes lipid nanoparticles (LNP) in its technologies to improve biosolubility and achieve more effective sustained-release properties to enable better dosage of active ingredients in patients, adds Dr. Huang.

Regarding the issue of using formulation or physical modifications, he says that such modifications can change solubility and enhance bioavailability, but a new chemical entity may be formed. If this occurs, additional toxicity studying must be conducted, which will add time and money to the development phase. Dr. Huang says: “Our technologies use current pharmaceutical science formulation approaches to improve solubility and bioavailability. This creates significant market value because our scientists don’t have to worry about physical modification of the chemical through the process. The benefit is that we can bring the drug to market with much less investment and in a shorter time, creating significant value.”

As an example, Dr. Huang points to ASD-005, a weakly basic cardiovascular drug with low solubility in aqueous media. Currently, it is only available as an oral dosage form. Ascendia developed an injectable nanoparticle formulation for use in an acute care setting. “Our scientists stabilized the drug substance in nanoparticle form using lipid excipients to enhance the drug loading and to achieve sustained release in vivo.”

The process that Ascendia developed involves the homogenous mixture of drug and lipids, then nanosizing the mixture in a parenteral grade vehicle. Prototype formulations were prepared with an average particle size of less than 100nm. A sustained-release PK profile with an enhanced bioavailability was achieved in an animal study over a 24-hour period after IV injection of the nanoparticle formulation. The control, a solvent-based solution, was rapidly cleared out of the body within a few hours.

BASF Pharma Solutions: Responding to the Shift in Solubilization Techniques

“Formulations and formulators worldwide are shifting their focus to solubilization techniques and formulations that are highly practical,” says Dr. Frank Romanski, Global Technical Marketing Manager, BASF Pharma Solutions. “Years ago, many formulations focused on nano-based methods of producing semi-stable suspensions and dispersions, requiring high quantities of solution or powder, impractically low concentrations of drugs, and multiple doses per patient per day. In 2019, this has shifted to using techniques like amorphous solid dispersions (ASDs) where 50%+ API is solubilized in a polymer matrix, and further processed into common tablets – clearly a practical solution.” Others work with lipid systems, like self-emulsifying drug delivery systems (SEDDS), which are easily encapsulated into soft or hard capsules for practical patient use.

Another shift he notes is from a batch-centric, highly specialized way of formulating to a strong focus on the overall processing. “For example, ASD formula-
tion through extrusion can be easily used as a bolt-on technology for continuous manufacturing, as the system functions essentially as powder-in and powder-out. With the rest of the pharma industry looking into continuous manufacturing, techniques that work within this approach will continue to grow in use.”

BASF’s specialization is in three core areas: amorphous solid dispersions (ASDs), lipid-based drug delivery systems (LBDDS), and liquid solutions. Liquid solutions, typically used in oral liquids and parenteral formulations are the simplest, where API is solubilized within high surfactant containing systems that solubilize the drug in colloidal structures like micelles for effective delivery via parenteral routes. Excipients used must have low immunogenicity, given the high concentrations required. BASF’s Kolliphor® HS 15 is an example. This surfactant contains many potent solubilizing characteristics of non-ionic ethoxylated surfactants, but exhibits a minimal immune response upon administration.

ASDs are a highly effective method of formulating poorly water-soluble drugs and developing them further into solid oral dosage forms. Using Hot Melt Extrusion (HME) or spray drying, the drug is solubilized into a polymeric matrix, such as Kollioden® VA 64 (copovidone). This highly effective strategy produces powder of ASD that can be readily processed into tablets.

Finally, LBDDS, and more specifically, self-emulsifying drug delivery systems (SEDDS) are a highly effective, commercially accepted method for formulating poorly water-soluble drugs. Through careful formulation, a microemulsion is formed with oil, water, and surfactant, which becomes a clear, low viscosity solution, ready for encapsulation into a soft or hard gel capsule.

Two BASF molecules, Kolliphor® HS 15 and Soluplus®, can be used to formulate a multitude of formulations with improvements in drug solubility and subsequent bioavailability. Both were recently approved in commercial formulations, Soluplus in the EU and Kolliphor HS 15 in the US.

BioDuro LLC: Enabled Formulations Bridge Discovery & Development

Success of an insoluble API depends on swift assessment of solubility challenges and rapid development of an enabling formulation to accelerate drug discovery and development timelines. There are ways to counter an insoluble API problem by using chemical or physical modifications.

“Chemical modifications are very useful in molecules that can be converted to a salt form or a pro-drug, but not all molecules are amenable to chemical changes,” says Ruchit Trivedi, Associate Director of Formulation, BioDuro LLC. “In those molecules that can be modified, chemical change can result in loss of activity. In such situations, it is necessary to pursue physical modifications of the molecule to improve kinetic solubility of the API.”

Amorphous dispersions – amorphous API in a polymer matrix – provide a sophisticated solution to solubility issues, says Dr. Trivedi. Conversion of crystalline API to amorphous form can increase the API’s kinetic solubility. Limited API availability during drug discovery reduces the extent of amorphous dispersion evaluation during discovery phase. “Micro-evaporative dispersions present an innovative and efficient solution to overcoming low API solubility during drug discovery and lead optimization,” he says. “With micro-evaporative dispersions, <1g of API is needed to evaluate several amorphous dispersion matrices. This can then be leveraged into downstream development or used for early pharmacokinetics studies to quickly eliminate potentially unsuccessful APIs during early discovery.”

BioDuro has developed the BioDuro Solution Engine that utilizes micro-evaporative dispersions in a streamlined process to screen an API with multiple polymers for solubility enhancement. Dr. Trivedi says this saves time during the development process and allows for rapid development and generation of sufficient material for in
vivo screening of amorphous dispersions, thereby increasing reliability of the process.

He says: “We have have successfully applied the micro-evaporative process to selection of matrices that provide enhanced solubility as well as controlled release functionality,” he says. “By utilizing API information from clients, knowledge gained through micro-evaporative dispersions, and in vivo expertise of our DMPK partners, the BioDuro Solution Engine can bridge the gap between discovery and development through rapid identification, development, and scale up of formulations.”

**Catalent Pharma Solutions: PBPK Modeling Uncovers Factors Leading to Poor Bioavailability & Solubility**

Lipid-based drug delivery systems, amorphous dispersions, particle-size reduction, and salts continue to be the gold standards for improving solubility of a drug molecule. “New excipients provide an opportunity to extend the functionality of current solubility-enhancing technologies,” says Ronak Savla, PhD, Scientific Affairs Manager, Catalent Pharma Solutions. “It is important that these new technologies address some of the shortcomings of current technologies if they are to reach commercial scale.”

Dr. Savla points to two major trends in the changing landscape of pharmaceutical development: increasing the percentage of drugs indicated for smaller patient populations; and more candidates from start-up companies accounting for a larger share of the pipeline. In both instances, the volume of API needed or available is limited compared to drugs developed by big pharma and for highly prevalent diseases.

“Many of our sites have employed material-sparing techniques to consume less API and use new strategies and technologies to extrapolate results and speed up development,” he says. “We also employ in silico prediction software to calculate the physicochemical characteristics of a molecule, which reduces the number of lab experiments.”

Recently, the Developability Classification System (DCS) was refined to be more applicable for early development when the drug dose may be unknown. Catalent utilizes physiologically-based pharmacokinetic (PBPK) modeling to uncover various factors that lead to poor bioavailability and solubility.

“It is not uncommon that drug developers realize that they have a bioavailability issue only after completing animal PK studies,” says Dr. Savla. “There is often a lack of data to elucidate the reason(s) for poor bioavailability. We want to understand if poor bioavailability is due to poor solubility, low fraction absorption, high first pass metabolism, rapid clearance, or a combination of these and other factors.”

The first step, he says, is to fill in the missing data on the API’s physicochemical characteristics: solubility in media and biorelevant buffers, crystallinity, purity, particle size and morphology. Poor solubility can be addressed with salt formation, formulation, and chemical modification. High first pass metabolism and rapid clearance can be addressed with higher and more frequent doses, but chemical redesign may be necessary.

**Evonik: Bringing Together Material Engineering & Formulation Development**

With more than 90% of actives currently in development considered to be poorly soluble or permeable, Evonik is seeing more customer projects for drugs with higher molecular weights and increased lipophilicity. “These customers will have often encountered challenges with basic technologies such as micronization and salt formation during the development of their early formulation concepts, says Dr. Jessica Mueller-Albers, Strategic Marketing Director for Oral Drug Delivery Solutions at Evonik. “Because these techniques are limited by the nature of the API, they can only influence the solubility rate and not the apparent solubility of the compound itself.”
As a specialist in advanced drug delivery, Evonik brings together material engineering and formulation development competencies, such as particle engineering, solid dispersions, and silica technologies to address poor permeability and optimize bioavailability.

For example, EUDRAGIT® polymers can dissolve APIs at the molecular level for stable, solid solutions, and have excellent processing characteristic, she says. “For spray drying, they are lightly soluble in common solvents and show excellent powder compressibility. For hot melt extrusion, they have excellent thermoplastic properties and broad miscibility with APIs and other excipients.”

She also recommends combining predictive tools like MemFis® for melt extrusion and formulation modeling to minimize development costs, as well as the early identification of suitable process technologies and formulation ingredients that can improve drug loadings and stability.

With an increasing number of poorly soluble compounds existing in the pre-clinical stage of development, Evonik has identified significant customer demand for rapid entry into clinical Phase I trials. For classical Phase I clinical trials, a fit-for-purpose formulation is required. However, for poorly soluble drugs, a conventional fit-for-purpose formulation is typically not possible. Therefore, Evonik has created a program for complex dosage forms that identifies the most appropriate technology for the customer’s API based upon a series of factors.

Lonza Pharma & Biotech: HPMC Capsules Provide Bioavailability Enhancement

Pharmaceutical companies are increasingly exploring and developing drugs with molecules that have solubility and/or bioavailability challenges. One way for drug developers to address these challenges is with functional capsules with physical and operational features. For example, a range of capsules exists that allow for either immediate release or controlled release of drugs for targeted delivery, or that provide enteric protection so the dosage form does not require additional coating. Both of these attributes enhance the functionality of formulations and protect them so that the optimal product reaches the patient. Capsules that impart these benefits act as functional excipients to enhance formulation efficacy.

Hypromellose (HPMC) capsules are an example of specialty polymers that can aid in bioavailability enhancement. HPMC
capsules containing no gelling systems are similar to gelatin capsules—dissolving quickly and predictably at different pH levels and dissolution media compositions—but also offer a lower moisture content than gelatin capsules, making them more suitable for hygroscopic and moisture-sensitive drugs and manufacturing processes, says Matt Richardson, PhD, Manager, Pharmaceutical Business Development, Lonza Pharma & Biotech Capsule Delivery Solutions. “Internal and external studies have shown that HPMC capsules can also provide increased bioavailability for some classes of molecules by sustaining supersaturated concentrations of dissolved drug in the gastrointestinal tract via crystallization inhibition,” he explains. “This is especially advantageous for drug forms such as high-energy salts and amorphous drug forms, as well as weakly basic drugs that are capable of supersaturating in the GI tract. HPMC capsules can also be specifically designed to be paired with enabling technologies like hot melt extrusion, furthering their potential for bioavailability enhancement.”

Capsugel® Vcaps® Plus capsules, from Lonza, are HPMC capsules that are suitable for moisture-sensitive ingredients, helping limit potential transfer of moisture exposure to API and working to enhance stability, Dr. Richardson says.

**Particle Sciences: Examining Bioavailability & Solubility Innovation from an Advanced Formulation Perspective**

Pharmaceutical scientists are always looking for ways to solve bioavailability and solubility issues related to delivering therapeutic payloads on target, on dose, and on schedule. Within the bounds of oral-solid dose forms, bioavailability and solubility issues are still resolved through a tried and tested set of formulation tools.

“However, although oral delivery for a broad range of APIs is well anticipated by popular non-proprietary methodologies, standard off-the-shelf solutions may not be enough for more challenging APIs,” says Robert Lee, PhD, President, Particle Sciences. “Without exploring alternative, more specialized formulation techniques, these actives may not progress through the development pipeline.”

Finding an effective method to dose more complex molecules may be less straightforward, but techniques do exist to successfully incorporate these actives into viable drug products. It is important to assess a range of technologies, ideally orthogonal, to address the molecule-specific challenges that become apparent during pre-formulation. Armed with the proper knowledge and tools, formulation scientists can narrow down the potential approaches to find a strategy that may maximize the delivery of poorly soluble drugs, and at the same time, achieve other drug product critical quality attributes, says Dr. Lee.

For example, Particle Sciences’ LyoCell® in-licensed technology combines a lipid-based approach with nanoparticles while leveraging reverse cubic-phase matrix. “This assures that the hydrophobic and hydrophilic domains in these nanoparticles are never more than a few nanometers apart and may lead to unique solubilization properties,” he says. LyoCell Technology uses GRAS ingredients and is intended for a range of applications and every route of administration.

In some cases, formulation and delivery methods alone may not be enough and it may be appropriate to modify the API. “For example, make it into a prodrug that could then be hydrolyzed into the corresponding active that delivers the desired biologic performance,” he explains. “This approach can create a defensible basis for intellectual property that may provide a drug developer a suitably viable and less risky approach.”

In the vast majority of cases, formulation and delivery technologies do provide an effective means to the therapeutic ends that Particle Sciences’ customers are seeking. “But it doesn’t work in every case,” Dr. Lee admits. “You have to have an open mind and do what the molecule requires to be formulated; be it formulation or chemical modification to successfully deliver the molecule and achieve the desired target product profile.”

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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.
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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 Seda, VP of Operations, and Tugrul Kararli, PhD, President & Founder, PharmaCircle

Introduction

The past decade has seen the unrelenting commoditization of drug delivery and formulation technologies. Technologies that a decade or two ago were considered breakthroughs and commanded premium pricing have become ‘off the shelf’ items. It has also resulted in part with a shift of the pharmaceutical industry’s focus away from small molecule therapeutics to biologics that address high value medical indications and provide extended market exclusivity. It has also coincided with a period where there have not been any ‘must have’ delivery technologies developed, for small molecules or biologics.

Until recently this new crop of macromolecule therapeutics has not required the benefits of drug delivery and formulation enhancement to distinguish themselves from competitors. This is likely to change as more companies face competitive ‘me-too’ biologics, biogenerics start to erode first generation product sales, and novel small molecule therapeutics are discovered that deliver comparable therapeutic benefits with simplified dosing protocols.

What’s needed is a renaissance in drug delivery and formulation technology development, the type that was seen four decades ago and lasted for the better part of thirty years. Drug delivery has had its greatest impact when it has identified whole new product ideas and delivered the necessary technologies. But this renaissance will require new ideas and the resources, financial and technical, to be realized. Are there really no big ideas beyond delivering macromolecules orally?

This four-part series looks at recent developments in the drug delivery and formulation sector with an emphasis on the past year. Data contained in these articles are drawn from the PharmaCircle Pipeline & Products Intelligence, FDA Product, EMA and PDMA modules that are sourced from public records with critical dissection of the data provided by PharmaCircle analysts. This first part looks at approvals in the three major world markets as a function of drug delivery and formulation parameters.
Biologics and Small Molecule New Molecular Entity approval numbers in 2018 approached parity

Table 1 – FDA Approval Numbers by Classification (2018)

<table>
<thead>
<tr>
<th>BLA</th>
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<tbody>
<tr>
<td>CDER</td>
<td>28</td>
</tr>
<tr>
<td>CBER</td>
<td>5</td>
</tr>
<tr>
<td>NDA (CDER)</td>
<td>128</td>
</tr>
<tr>
<td>Type-1</td>
<td>36</td>
</tr>
<tr>
<td>Type-2</td>
<td>4</td>
</tr>
<tr>
<td>Type-3</td>
<td>23</td>
</tr>
<tr>
<td>Type-4</td>
<td>10</td>
</tr>
<tr>
<td>Type-5</td>
<td>40</td>
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<tr>
<td>Type-10</td>
<td>2</td>
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<tr>
<td>Type-1/4</td>
<td>5</td>
</tr>
<tr>
<td>Type-3/4</td>
<td>5</td>
</tr>
</tbody>
</table>

Source: PharmaCircle Pipeline & Products Intelligence and FDA Products Module

- Biologics, 351(a) and 351(k) approvals, achieved a new high in 2018 with a total of 34 therapeutic product approvals versus 17 in 2017
- A total of 9 Biosimilar, 351(k), approvals were granted by the FDA in 2018 versus 5 in 2017
- Of the 19 Novel Drug Approval Biologics approved by the Drugs Division, 11 were granted Priority review and 12 were classified as Orphan drugs
- Non-biological Novel Drug Approvals, single active and combination products, totaled 41 in 2018, an increase on the 34 approved in 2017
- New Dosage Forms totaled 28, including 23 sole active and 5 new combination products
- New Formulation or Manufacturer approvals totaled 40 but often related to relatively minor formulation changes and multisource injectable approvals

Table notes: Multisource injectables are approved through the NDA rather than the ANDA regulatory process and can unintentionally skew the new drug approval figures. Type-5 approvals are not considered in the analyses presented on the following pages.
Injection Route approvals continue to gain share with the increasing development and approval of Biologics

Table 2: 2018 approvals by Administration Route

<table>
<thead>
<tr>
<th>Delivery Route</th>
<th>FDA (n=113)</th>
<th>EMA (n=69)</th>
<th>PMDA (n=54)</th>
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</thead>
<tbody>
<tr>
<td>Injection</td>
<td><strong>40</strong> (35%)</td>
<td><strong>36</strong> (52%)</td>
<td><strong>21</strong> (39%)</td>
</tr>
<tr>
<td>Infusion Intravenous</td>
<td>19</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Infusion / Injectable Intravenous</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Injectable Intramuscular</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Injectable Intravenous</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Injectable Subcutaneous</td>
<td>15</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Injectable Intralesimal</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Injectable Subretinal</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Multiple / Other</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Instillation/implantation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inhalation</td>
<td><strong>4</strong> (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
<td><strong>1</strong> (2%)</td>
</tr>
<tr>
<td>Oral</td>
<td><strong>59</strong> (52%)</td>
<td><strong>30</strong> (43%)</td>
<td><strong>29</strong> (54%)</td>
</tr>
<tr>
<td>Sublingual</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Surgical insertion</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Topical</td>
<td>5 (4%)</td>
<td>0</td>
<td><strong>2</strong> (4%)</td>
</tr>
<tr>
<td>Transdermal</td>
<td>0</td>
<td>0</td>
<td><strong>1</strong> (2%)</td>
</tr>
<tr>
<td>Vaginal</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: PharmaCircle Pipeline & Products Intelligence and FDA Products Module

- While the absolute number of Injection delivered products is similar for the FDA (19) and EMA (18), the difference in relative percentages is skewed by a much larger number of Oral aroute approvals in the US
- The distribution of approvals in Japan is more similar to the FDA than the EMA
- Notable by their absence are Nasal route products in all territories. The likely approval of nasal esketamine for severe depression in 2019 could offer new life to the Nasal sector
- There was only one new Transdermal route product approved in the three markets. This is consistent with a longer-term trend of limited novel transdermal product approvals
- After a few years of multiple annual approvals there was only one sublingual route new product approval by the FDA in 2018

Table notes: The figures above do not include Type-s Approvals (FDA), New Dosage Form supplements (FDA), Tentative Approvals (FDA) or Biosimilars (all).
Drug Delivery and enhanced formulation approvals are on the wane

Table 3 – 2018 approvals by Drug Delivery Category

<table>
<thead>
<tr>
<th>Category</th>
<th>FDA (n=113)</th>
<th>EMA (n=69)</th>
<th>PMDA (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adeno-Associated Virus Vectors</td>
<td>0</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Biodegradable - All</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conjugates – All</td>
<td>6 (6%)</td>
<td>4 (6%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Inhalation</td>
<td>4 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dry Powder Inhalers</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liquid Inhalers/Nebulizers</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Injection – Device Related</td>
<td>12 (10%)</td>
<td>8 (12%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Autoinjectors / Pens</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Prefilled Syringes</td>
<td>9</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Injection Other</td>
<td>19 (17%)</td>
<td>19 (28%)</td>
<td>12 (22%)</td>
</tr>
<tr>
<td>Ocular - All</td>
<td>2 (2%)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Implant</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oral</td>
<td>59 (52%)</td>
<td>30 (43%)</td>
<td>29 (53%)</td>
</tr>
<tr>
<td>Formulation Enhanced</td>
<td>10 (9%)</td>
<td>4 (6%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Other / None</td>
<td>49</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Prodrugs - All</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Topical - All</td>
<td>5</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other - All</td>
<td>6</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

Source: PharmaCircle Pipeline & Products Intelligence and FDA Products Module

- Most notable is the relative lack of drug delivery and formulation enhanced approvals, ranging from oral to injectable.
- In terms of injectables, many of the products approved in 2018 are targeted to Orphan indications and used in a specialty care setting where enhanced self-administration is less important.
- In the case of oral products there are fewer opportunities for simple formulation enhancements of previously approved actives. Oral actives are being selected on the basis of inherently more attractive pharmacodynamic properties and not in need of formulation improvement.
- Not explicitly apparent in the table above is the absence of any approvals of abuse resistant modified release products using physical methods. One product using a prodrug approach, Apadaz, was approved but without abuse deterrent labeling. This may suggest the market is well serviced by existing products, a perceived lack of commercial potential for these products, or simply less regulatory appetite for these products.
- Only one new Class II, III or IV opioid was approved by the FDA in 2018, a controversial dispenser version of sufentanil for sublingual administration.

Table notes: The figures above do not include Type-5 Approvals (FDA), New Dosage Form supplements (FDA), Tentative Approvals (FDA) or Biosimilars (all).
Approvals are increasingly associated with simpler dosage forms (Solutions and Tablets)

Table 4 – 2017 Approvals by Dosage Form

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>FDA (n=112)</th>
<th>EMA (n=69)</th>
<th>PMDA (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalation Powder</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inhalation Solution</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Inhalation Suspension</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Injection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection or Suspension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emulsion</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Lipid Complex</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Lyophilized Powder for Solution</td>
<td>8</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Lyophilized Powder for Suspension</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Powder for Solution or Suspension</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Solution</td>
<td>28</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Suspension</td>
<td>1</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Ophthalmic Emulsion or Solution</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Emulsion or Solution</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vaginal Insert or Ring</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsule</td>
<td>11</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Powder for Solution</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Powder for Suspension</td>
<td>2</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Soft Gel Capsules</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Solution</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Suspension</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tablet</td>
<td>38</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Tablet for Solution</td>
<td>0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Film</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sachet/Granules</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Topical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foam</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gel</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Lotion</td>
<td>2</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Patch</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Solution</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sublingual</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Transdermal</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Vaginal Insert or Ring</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

Source: PharmaCircle Pipeline & Products Intelligence and FDA Products Module

- Tablet, capsule and injection solutions accounted for 62% (147/236) of new product approvals in the three markets
- By market, these three dosage forms accounted for 68% of all new drug approvals by the FDA, 62% by the EMA and 50% of PMDA approvals
- Of the tablet and capsule dosage form approvals only 21% (21/101) of new product approvals involved any type of drug delivery or formulation enhancement with the majority of these approved in the USA

Table notes: The figures above do not include Type-5 Approvals (FDA), New Dosage Form supplements (FDA), Tentative Approvals (FDA) or Biosimilars (all).
There is remarkable consistency in approvals by Molecule Type across the major markets

Table 5 – 2018 approvals by Molecule Type

<table>
<thead>
<tr>
<th>Type</th>
<th>FDA (n=113)</th>
<th>EMA (n=69)</th>
<th>PMDA (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Active</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody</td>
<td>95 (84%)</td>
<td>60 (87%)</td>
<td>47 (87%)</td>
</tr>
<tr>
<td>Antibody / Protein (Fusion)</td>
<td>1 (1%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antibody / Small Molecule (Conjugate)</td>
<td>-</td>
<td>1 (9%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>1 (1%)</td>
<td>-</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Cell Therapy</td>
<td>-</td>
<td>3 (4%)</td>
<td>-</td>
</tr>
<tr>
<td>Gene Therapy</td>
<td>-</td>
<td>1 (1%)</td>
<td>-</td>
</tr>
<tr>
<td>Peptide</td>
<td>-</td>
<td>2 (3%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Peptide / Small Molecule (Conjugate)</td>
<td>1 (1%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Polymeric</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>-</td>
</tr>
<tr>
<td>Polymeric / Protein (Conjugate)</td>
<td>4 (4%)</td>
<td>2 (3%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Protein</td>
<td>6 (5%)</td>
<td>7 (9%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>siRNA</td>
<td>2 (2%)</td>
<td>2 (3%)</td>
<td>-</td>
</tr>
<tr>
<td>Small Molecule</td>
<td>65 (55%)</td>
<td>30 (43%)</td>
<td>29 (54%)</td>
</tr>
<tr>
<td>Multi Active</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small Molecules (2)</td>
<td>18 (16%)</td>
<td>9 (13%)</td>
<td>7 (13%)</td>
</tr>
<tr>
<td>Small Molecules (2 or 3) / Polymeric</td>
<td>9 (8%)</td>
<td>7 (10%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Small Molecules (3)</td>
<td>1 (1%)</td>
<td>-</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Small Molecules (4)</td>
<td>6 (5%)</td>
<td>2 (3%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

Source: PharmaCircle Pipeline & Products Intelligence and FDA Products Module

- Biologics accounted for one third (78/236) of non-generic new product approvals in 2018. In the USA this figure rises to 57% if only new molecular entities are considered.
- Antibody related approvals accounted for 49% (38/78) of the biologics and macromolecule approvals in 2018. Not surprisingly, multi active (fixed dose combination) product approvals were limited to small molecules.
- Onpatro’s approval by the FDA and EMA represented the first approvals of a small interfering ribonucleic acid (siRNA).
- At this point biologics are largely used separately when combination therapy is deemed appropriate.

Table notes: The figures above do not include Type 5 Approvals (FDA), New Dosage Form supplements (FDA), Tentative Approvals (FDA) or Biosimilars (all).
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Marc Iacobucci, BS, Clinical Pharmacy, MBA Officer & Board Member, NanOlogy, LL
Local Delivery of Submicron Taxane Particles: Increased Tumor Kill & Surprising Immune Response

Emer Leahy, PhD President & CEO
PsychoGenics Inc.
High Content Phenotyping & Machine Learning Offer New Approaches to Drug Discovery

Pascale Diesel, PharmD Vice President, Life Sciences Practice, CRA
Adopting New Strategies to Support Cell & Gene Therapy Development

Srini Anandakumar
Senior Director of Clinical Analytics Innovation, Saama Technologies
Building a Next-Generation Clinical/Scientific Data Management Solution

Ashleigh Palmer, MBA CEO & Co-Founder, Provention Bio
Challenging the Drug Development Paradigm With interception & Prevention - How & Why

Inayet Ellis, PhD, Scientific Affairs Manager, Gattefosse USA, Pharmaceutical Division
Overcoming the Challenges of Oral Delivery of Peptides

Eugene Polini
Technical Key Account Manager Datwyler
Chlorine Dioxide Sterilization Effects on Elastomeric Closure (FM457/0 With & Without Omni Flex) Physicochemical & Functional Characteristics

Marlene Leuenberger
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ABSTRACT

At the recent American College of Neuropsychopharmacology (ACNP) meeting, Sunovion Pharmaceuticals and PsychoGenics Inc. announced positive Phase 2 results for SEP-363856, a novel, first-in-class treatment that has the potential to offer patients with schizophrenia the chance to live a near-normal life. Available treatment options fail to treat all schizophrenia symptoms, and their side effects result in non-compliance and relapse. SEP-363856, by contrast, shows robust effects across a broad range of disabling symptoms, including positive, negative, depressive, and general psychopathology symptoms, with a safety profile similar to placebo. Discovered via SmartCube®, PsychoGenics’ target-agnostic platform, SEP-363856 does not interact with the dopamine D2 or other neuroreceptors thought to mediate the effects of currently available antipsychotic agents. The SmartCube platform thus represents a novel approach to discovering the next generation of breakthrough treatments for schizophrenia and other neuropsychiatric disorders.

INTRODUCTION

Neuropsychiatric disorders impact hundreds of millions of patients, many of whom have poor or no treatment options. Yet, despite the enormous human cost and societal burden, there are almost no new mechanisms to treat major neuropsychiatric disorders in decades. Instead, we rely on old drugs, some with serious side effects. The main reason for this situation is that the target-based approach of identifying highly selective targeted compounds has failed to deliver new and improved treatments for central nervous system (CNS) disorders. Consequently, the approval rates for new CNS drugs are significantly below the average success rates of other therapeutic areas. Faced with generic competition and rising costs of drug discovery and development, many big pharma companies have abandoned psychiatric drug discovery. The target-driven approach relies on understanding the human genetics of a disease. However, neuropsychiatric disorders are infinitely complex, involving multiple symptom domains that are not associated with a specific gene mutation. Instead, there are multiple susceptibility genes, epigenetic factors, compensatory mechanisms, and significant environmental factors (stressors) that contribute to these disorders, resulting in dysfunctional neurocircuitry and atypical behavioral/functional output. Neuropsychiatric symptom domains, which are broadly classified into emotion, cognition, motivation, and social behavior categories, permeate multiple psychiatric disorders, and the presentation and severity of symptoms may vary considerably even for the same disorder. Recognizing this complexity, the National Institutes of Health (NIH) has established a research framework known as the Research Domain Criteria (RDoC, https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml), to enhance understanding of neuropsychiatric disorders in terms of psychological/biological systems associated with symptom domains, and to relate those symptom domains to neurocircuitry and genetics.
PHENOTYPIC SCREENING

The alternative to target-driven drug discovery is a phenotypic systems approach, which can deliver treatments that work via novel, unknown, or multiple mechanisms. Phenotypic screening strategies have been more productive than target-based approaches, especially for CNS disorders, as illustrated by Swinney and Anthony’s seminal 10-year survey (1999-2008), which found that 87.5% of new, first-in-class CNS treatments were discovered phenotypically.1 There is an industry-wide push to bring in vivo data into the drug-discovery process earlier so researchers can make more informed decisions early on, thereby positively impacting success rates and reducing discovery time.7-10

SMARTCUBE®

The SmartCube platform offers an unbiased way to industrialize phenotypic drug discovery for CNS disorders by screening compound libraries in a manner that is agnostic to mechanism, thus often resulting in novel pharmacology.11-16 SmartCube is an automated testing platform that presents a sequence of challenges to a mouse through its customized hardware, incorporating computer vision and artificial intelligence to extract behavioral, physiological, and telemetric features. The system offers several advantages over standard behavioral testing, including:

- High throughput — can screen tens of thousands of compounds for CNS activity and identify those with behavioral/physiological profiles that are redolent of drugs that treat a specific neuropsychiatric disorder;
- High content — collects millions of measures and thousands of features, and employs proprietary machine learning algorithms to detect subtle phenotypic differences (often not seen with standard tests) associated with a disease model or drug effect; and
- Unbiased — computer vision algorithms and artificial intelligence eliminate human intervention and subjectivity.

Although SmartCube collects approximately half a million data points per mouse per session, it uses behavioral definitions and machine learning techniques to reduce a dataset to approximately 2,000 features (Figure 1). The system enables testing of novel compounds and disease models by comparing these compounds’ complex behavioral/physiological profiles to those from a large database of marketed drugs used to treat the spectrum of disabling neuropsychiatric diseases.

The SmartCube platform applications include:

- Screening representative compounds from chemically diverse libraries in a target-agnostic approach to find compounds that interact with novel or multiple targets;
- Screening target-focused libraries to determine the therapeutic utility of a target
or to identify a preferred chemotype;

- Repurposing compounds that are discontinued (for reasons other than safety) or currently being developed for other non-CNS indications;

- Assessing compound combinations to determine the efficacy of a combination of novel compounds or a novel compound combined with an existing marketed drug;

- Lead optimization to identify more potent and/or safer compounds; and

- Detecting side effects through assessment of broad dose responses.

The SmartCube hit rate (hits are defined as having at least 70% activity in SmartCube at a single dose) is approximately 20% for a diverse library. The hit rate is high relative to typical high-throughput screening at single targets (typically 0.1%). Compound hits then undergo a series of steps to:

- select compounds with the desired signature/devoid of side effects;

- assess potential patentability around the chemotype;

- eliminate undesirable targets such as hERG and/or to show the absence of classical targets;

- determine whether the compound differentiates from existing treatments (eg, antipsychotics that improve negative symptoms or cognition); and

- establish a translational biomarker, a tool that can be employed to demonstrate that the compound is getting to the brain and having an effect (eg, EEG or MRI).

Compounds that pass those hurdles proceed to lead optimization. At this stage, analogs of the lead compound are made and tested in SmartCube to identify compounds with improved potency or to eliminate a possible side effect. Using an in vivo readout allows rapid assessment of modifications to a pharmacophore, and preserving the behavioral signatures means the compound is hitting targets in the brain. Compound screening and optimization in SmartCube are highly efficient; the system typically enables identification of a pre-development candidate from fewer than 300 compounds, a process that can be completed in under a year, a success rate that not only saves considerable time and money, but also patient lives.

In addition to the SmartCube signatures for the thousands of compounds tested, PsychoGenics has tested several disease models (including models of Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis (ALS), and depression) in SmartCube to identify the critical features that are responsible for the phenotype. This approach is invaluable in finding robust and early phenotypes for many CNS disorders. Knowing the features that define a disease model means we can mine the thousands of tested compounds and identify treatments predicted to reverse the disease-specific features and later test and confirm those predicted treatments in the model.

PARTNERSHIPS

PsychoGenics has entered into shared-risk partnerships with several pharma and biotech companies to help identify a new generation of treatments for neuropsychiatric disorders. Due to its target-agnostic nature, the SmartCube approach has increased the probability of successfully finding drug candidates with novel, first-in-class mechanisms of action and improved side-effect profiles, making them suitable for treating the symptoms of neuropsychiatric disorders. In the Sunovion
partnership, PsychoGenics evaluated a library of thousands of compounds, leading to the joint discovery of several new drug candidates with novel modes of action, including SEP-363856.

SCHIZOPHRENIA - SEP-363856

The development of SEP-363856 has potentially profound implications for the 0.3% to 0.7% of people living with schizophrenia. In addition to experiencing the so-called positive symptoms of hallucinations and delusions, patients with schizophrenia often lose motivation and interest in social activities, become socially isolated, and find it difficult to experience pleasure in everyday life; these latter effects are commonly referred to as the negative symptoms of the disease. Notably, unlike currently available schizophrenia treatments, which are effective in treating some of the positive symptoms but not the negative symptoms, SEP-363856 appears to improve both types of symptoms. In a double-blind, placebo-controlled Phase 2 trial involving 245 patients with schizophrenia, SEP-363856 was associated with a statistically significant and clinically meaningful improvement in the Positive and Negative Syndrome Scale (PANSS) total score compared to placebo after four weeks of treatment (-17.2 vs. -9.7, respectively; p=0.001). Patients treated with SEP-363856 also showed improvement in the overall severity of illness as assessed by the Clinical Global Impression — Severity scale (CGI-S) (p<0.001). In addition, SEP-363856 was associated with improvement in all major PANSS (positive, negative and general psychopathology) (p<0.02) subscales. Additionally, SEP-363856 was well tolerated in the trial, with an overall discontinuation rate that was comparable to placebo. Adverse events including extrapyramidal symptoms (slowed movements, stiffness or tremor) were also comparable to placebo. By contrast, current schizophrenia treatments have severe side effects, including sedation, akathisia/movement disorders, and weight gain, which cause many patients to discontinue treatment and increase the probability of a relapse.

The recent Phase 2 clinical trial was designed, conducted and supported by Sunovion Pharmaceuticals, as part of the SEP-363856 global development program. Patients who completed the Phase 2 trial were eligible to continue in an open-label, long-term extension study, which is currently ongoing. SEP-363856 is also currently being studied as a treatment for Parkinson’s disease psychosis. Additional studies are planned and additional indications are under consideration in the hope that SEP-363856 will soon be available to patients suffering from severe disabling mental illnesses.

REFERENCES


Dr. Emer Leahy is CEO of PsychoGenics Inc., a profitable preclinical CNS service company. She earned her PhD in Neuropharmacology from University College Dublin, Ireland, and her MBA from Columbia University. She also serves as Adjunct Associate Professor of Neuroscience at Mount Sinai School of Medicine. Dr. Leahy has more than 25 years of experience in drug discovery, clinical, and business development for pharmaceutical and biotechnology companies, including extensive knowledge of technology assessment, licensing, mergers and acquisitions, and strategic planning. Dr. Leahy served on the Emerging Companies Section for the Board of Directors of the Biotechnology Industry Organization (BIO). She currently serves on the Board of Directors of Intensity Therapeutics, the Business Review Board for the Alzheimer’s Drug Discovery Foundation, and the Scientific Advisory Board of the International Rett Syndrome Foundation. She can be reached at emer.leahy@psychogenics.com.
Established in 1993, SK Life Science, Inc., is a subsidiary of SK Biopharmaceuticals, Co., Ltd., focused on developing and commercializing treatments for disorders of the central nervous system (CNS). Both companies are a part of the global conglomerate SK Group, the second largest company in South Korea. SK Group generated more than $108 billion in revenue in 2016. In November 2017, SK life science announced the launch of its commercial corporate presence in the US, restating its commitment to making a difference in the lives of people suffering from CNS diseases. Currently, the company has a pipeline of six products in development for the treatment of CNS disorders, including epilepsy, sleep disorder, and attention deficit hyperactivity disorder, and has already initiated 16 Investigational New Drug (IND) applications with the US FDA. Its lead product, cenobamate (YKP3089), is a Phase 3 investigational compound that is being studied as a potential treatment for patients with partial-onset seizures. Drug Development & Delivery recently interviewed Sebby Borriello, Vice President & Chief Commercial Officer, to discuss the challenges and trends surrounding development of therapies for neurological diseases.
Q: Can you please provide an overview of SK life science for our readers?

A: SK life science, which is based in South Korea, announced the launch of its commercial corporate presence and infrastructure in the US in November 2017. We are growing quickly, and have US headquarters in Fair Lawn, NJ.

With a pipeline of six products in development for the treatment of CNS disorders, including epilepsy, sleep disorder, and attention deficit hyperactivity disorder, the company has already initiated 16 Investigational New Drug (IND) applications with the US FDA. Our lead product, cenobamate (YKP3089), is an investigational compound that is being studied as a potential treatment option for patients with partial-onset seizures.

We also have established a highly blood-brain, barrier-permeable, unique compound library and translational screening system that has been clinically proven in the field of CNS disorders throughout the past 20 years.

Through everything we do, we are working to redefine the future of CNS therapies with products that we believe will truly make a difference in the lives of patients.

Q: How does SK life science plan to make a meaningful impact on patients and fulfill unmet medical needs?

A: In the US, there remains significant unmet need for patients with CNS disorders, particularly epilepsy, with a minimum of 3.4 million people living with epilepsy in the US alone. Despite the addition of several new treatment options throughout the past 5 years, approximately one-third of the epilepsy patient population continues to have seizures. Even more troubling is the fact that this one-third figure has remained relatively constant throughout the past several decades. The SK life science team is firmly committed to making a difference in the lives of people suffering from epilepsy.

Furthermore, due to high regulatory standards, several large pharmaceutical companies have decreased investment in the CNS industry. However, SK life science recognizes the critical unmet need, and we are committed to working tirelessly in search of solutions for this patient population.

These patients’ needs drive our steady commitment to this medical community and have inspired our development of the compounds in our pipeline, including early stage treatment candidates for epilepsy, attention deficit hyperactivity disorder, Parkinson’s disease, and cognitive impairment associated with schizophrenia.

Q: How is SK life science evolving in the industry, and what’s different about its drug development plans and pipeline approach?

A: We have a group of scientists, inventors, and explorers working to unlock the complex mysteries of the brain in the increasingly stagnant CNS space, with the goal of creating novel, small-molecule compounds from the ground up. We are uniquely positioned in the industry, as we are focused on developing novel treatments instead of reformulations of existing drugs.

SK life science has more than 20 years of experience partnering with pharmaceutical companies on licensing and development agreements. For example, we have a partnership with Jazz Pharmaceuticals for its late-stage project, solriamfetol, for the treatment of excessive sleepiness in adult patients with narcolepsy and obstructive sleep apnea. Although Jazz acquired the license to develop and commercialize the drug, SK Biopharmaceuticals retains the rights in 12 major Asian countries, including South Korea, Japan, and China, and we have plans to develop and commercialize it in the Asian market moving forward.

We’re now at a pivotal point for the company as we prepare to commercialize meaningful products here in the US market.

Q: What are the biggest company milestones expected this year for SK life science?

A: Cenobamate is our biggest focus right now, and we have a pivotal Phase 3 global clinical trial underway. We expect to move cenobamate through the regulatory approval process and market it ourselves. We hope to file for marketing authorization to the US FDA as early as late 2018.
Q: Can you please describe the challenges biopharmaceuticals face in the neurological disease space?

A: When compared to other disease categories, the neurological disease space hasn’t seen the same robust development – especially in the past few years. It’s stagnant, and that’s largely because, from our perspective, the brain remains one of the most difficult organs in the body to target with safe and effective medicines. The result is that more and more companies are moving into other areas of R&D, with oncology being perhaps the best example. We believe this leaves SK life science with both an opportunity and a responsibility to fill this substantial unmet need. Specifically, we’ve seen physician surveys that show they perceive effective therapies for treatment-refractory epilepsy as the greatest unmet need in epilepsy.

However, at the same time, we believe the FDA has provided clear guidance on how sponsors should approach clinical trials for epilepsy therapies. The agency has also given guidance that allows sponsors to expand treatments for monotherapy indications and to pediatric patients by extrapolating results from adult trials. This could eliminate the need for large and potentially complex trials, and speed access to treatment options.

Q: SK life science is new to the US. From your perspective, why is there an influx in companies with global headquarters or parent companies in Asia creating business units in the US?

A: Asian-based biopharmaceutical companies are increasingly seeking global growth opportunities, particularly in the US drug market. By establishing R&D and commercial operations in the US, SK Biopharmaceuticals has made the necessary steps to progress our CNS drug pipeline and act as a leader in this movement.

We see our global experience in SK’s other businesses and further expansion as an asset during this time of rapid building of our clinical and commercial organization in the US.

Q: How does a company based in South Korea plan for the challenges of establishing a US-based organization, from areas like geographical distance to infrastructure and culture?

A: SK life science knows the importance of an integrated team, and we make it a priority. Leadership in the US and Korea collaborate every day to ensure employees are aligned on all projects.

We’re using the global experience we already have to rapidly build our US clinical and commercial infrastructure. We have a team of more than 70 people with decades of experience researching and commercializing drugs in the states, and plan to continue expanding this workforce in 2018 and beyond as we move toward the approval and launch of the late-stage products in our pipeline.

By establishing a US footprint, we have strategically increased the company’s flexibility in how we approach commercializing products and forming business partnerships. We have positioned SK life science with the infrastructure and expertise needed to launch potentially novel compounds like cenobamate with our own company resources, and also recognize that our US presence provides us broader partnership opportunities.

Q: Why commit to developing cenobamate (and other medicines) in the US, which has very complicated regulatory and commercial systems? Does this not present added challenges?

A: At SK life science, we believe our experience and development expertise gives us the unique opportunity to succeed and provide new options for patients, including our investigational compound, cenobamate, for the potential treatment of epilepsy.

Bringing safe and effective new medicines to patients is rightfully complex regardless of what country we operate in. The US has its own unique requirements for drug approvals, particularly in CNS, where relative to other areas, drug development is limited and regulatory standards are high.

We are focused on researching, developing, and commercializing therapies for CNS disorders, no matter the cost. The significant unmet need for patients is what keeps us going.
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It can be tempting to explore completely new business directions based on radical innovations from full-blown, large-scale AI applications. Over-ambitious AI efforts in drug discovery remain risky and have shown few game-changing benefits. However, by treating AI as one more tool within a broad data quality toolkit, and by focusing narrowly on specific research and business bottlenecks, it is possible to efficiently bring real practical benefits to research and business.

Can AI make a difference for drug discovery efforts, or will the industry waste time and money on another hype cycle? There are many benefits that can be achieved from AI today at low cost and with virtually no risk. By combining traditional data quality and analysis capabilities with AI applications, drug discovery research can benefit through reduced time and cost to achieve practical goals. AI has the potential to make a positive difference in drug discovery, development, and delivery.

The following will briefly discuss main trends in AI for drug discovery before describing some basic data quality applications that can be useful in drug research.

AI has struggled to hit home runs that completely transform the healthcare industry, for example, by creating virtual doctors that can diagnose and prescribe. However, less ambitious solutions to bottlenecks that can block research - such as data identification, extraction, quality, harmonization, and integration - are seeing real benefits.

Drug discovery research goals can benefit through improved data quality at reduced time and cost. By focusing AI on narrower but challenging and time-consuming bottlenecks, researchers have been able to reduce time and cost to identify, extract, harmonize, and integrate drug-related data. AI-enabled technologies combined with traditional data quality processes are finally moving drug discovery and precision medicine past data quality issues that have plagued biotechnology and pharmaceutical industries for decades.
COMBINING TRADITIONAL & ADVANCED TECHNOLOGIES

General AI methods include machine reasoning (MR) and machine learning (ML). First, MR builds on newer (NoSQL, Graph, and Semantic) AI-enabling database technologies to provide expert systems. MR applies semantically meaningful data models or “ontologies,” used for deductive reasoning, entailment, and decision support, even with incomplete datasets. ML applies various statistical analyses for training and learning using example datasets with features (eg, variables) and outcomes (eg, results). Next, ML applies supervised and unsupervised algorithms to analyze these training datasets, to identify features that are, or seem to be, related to outcomes for inductive hypothesis generation and to facilitate pattern identification for decision support.

Traditional methods for improving data quality in drug discovery include rules-based data quality assessment and transformation, normalization of drug terms to standardized lists or “lexicons” via scored string matching, and finally, statistical analyses of data quality. Combining the two approaches, however, creates a new and modern way of solving drug development problems. The key is to apply these technologies in focused and well-defined applications, resulting in a smarter kind of data tool.

MAKING AI PRACTICAL VIA SPECIFIC APPLICATIONS

Ideally, AI can be applied to enhance narrowly defined applications, including drug terminology normalization, enrichment of existing drug data with published information, and master data integration and management. Perhaps most importantly, core technologies that can deliver these capabilities, even when applying AI under the hood, can be delivered to the industry in convenient and accessible ways.

Example applications include cloud-based transformation APIs (specific data quality and enrichment applications); drug content resources (look-ups and knowledge hubs); and master data management (environments, workflows, databases for data extraction, harmonization, linking, search, and management). These resources make use of traditional and advanced technologies to reduce time and cost required to achieve comprehensive, clean, harmonized, standards-compliant drug data that is effectively linked to the life science data required to meet scientific and business goals today.

Let’s take a look at a few example applications of AI that have shown immediate practical benefits for drug discovery and development.

COMBINING MR WITH TRADITIONAL METHODS FOR IMPROVED DATA QUALITY AT REDUCED COST

Data quality has presented endless challenges in drug research and discovery, development and delivery. These challenges can be overcome efficiently by bringing the best of the old and new to solve practical data quality problems.

Basic issues like diverse standards for chemistry terminology can cause research and business bottlenecks. For example, in the US, the FDA requires one set of preferred terminology for submissions (such as those based on National Drug Code or NDC), but different drug discovery research also requires attention to diverse standards and data sources, including RxNorm, ChEBI, and ChEMBL, to ensure that data definitions and terms are most useful for different purposes. Traditional methods, such as standardized lexicons with synonyms and preferred terms, can often be applied to easily transform data from one standard lexicon to another.

However, cleaning up and standardizing drug terminology using traditional methods is only the first step. AI, such as MR, can be applied to solve data quality issues including:

- Identifying data, to extract useful content from documents or dirty databases
- Assigning data, to correct classes and relationships for data integration
- Enriching data, to fill in gaps with new information

How can AI fill in gaps on incomplete datasets? Ontologies from MR can be applied to create entailments, or processes that make new assertions about data based on reasoning. Let’s look at a simple example.

A researcher has a drug database with compounds and associated biological activities and mechanisms. However, there is no drug-drug interaction information.

With the database modeled in Figure 1, researchers can’t ask if these two drugs are contraindicated. Adding an ontology and MR capabilities to the environment can bring broad benefits to research.

Specifically, adding an ontology with
semantic assertions makes reasoning possible (Figure 2). The database “knows” that Selegeline is an MAOI and Phenylephrine is an AR Agonist. The ontology for MR knows that MAOIs and AR Agonists are contraindicated. By bringing ontology-enabled MR to the database, we can infer that Selegeline is contraindicated with Phenylephrine. With reasoning and entailment, we can add that information to create a new, richer database (Figure 3).

It is increasingly easy for knowledge engineers and other advanced data scientists to access and apply traditional lexicons along with advanced semantic ontologies and MR to, for example, curate and integrate internal research with public content. However, these aren’t tasks for drug researchers.

Benefits for research can be delivered simply. For example, end users can plug into APIs or use web-based look-ups that apply AI quietly in the background to transform inconsistent lists of drug terms and metadata into comprehensive datasets with standardized terminology and rich information.

Uploading a messy list of drug terms and receiving validated, standardized, and enriched results within seconds can be very useful. For example, uploaded “dirty” terms can be automatically mapped to the FDA’s preferred terms, with additional data added according to interest, such as NDC codes, proprietary and generic names, FDA Product IDs, labeler names, routes, dosages, and associated biological mechanisms. Combining traditional list-based standardization with MR to identify and ensure correct matches and to enrich existing data reduces time and cost to achieve clean, rich, usefully connected data.

Check and verify that you are using preferred, correct terms for your drug or list of drugs in order to harmonize your data and comply with terminology standards.

Validate millions of pharmaceutical names, variants, dosages, and spellings against a pharmacopeia to save time, clear confusion, and mitigate errors.

COMBINING ML & MR FOR IMPROVED RESEARCH

Traditional and semantic MR technologies have made it possible for vendors to integrate information from hundreds of public data sources, about hundreds of thousands of drugs and potential new drugs, including content from massive databases and peer-reviewed journal resources.

Comprehensive reports from clean, internally integrated data and from integrated public data can provide deep information about your company’s drugs, competitors’ drugs, concomitantly prescribed drugs, contraindicated drugs, as well as relationships between drugs, genes, proteins, and diseases. But how can AI impact your basic research?

FIGURE 2

This small ontology, or model of resources and relationships that define an area of interest, asserts that MAOIs are contraindicated with AR agonists.
By combining ML with MR, it becomes possible to gain a deeper understanding of data:

- Harness the power of ML to identify related variables and uncover patterns in data
- Reduce data dimensionality to identify and focus on the information that makes a difference
- Segment and consolidate information to classify drug general usage or bioequivalence at prescription
- Harness the power of combined general AI by applying MR to transform correlated data from ML into explanatory, causally meaningful information

ML is a more familiar form of AI. While MR requires knowledge and expertise to create and apply general ontologies to specific data challenges, MR requires clean, integrated data, particularly variable features and target outcomes. ML commonly requires training, usually in the form of acceptance or rejection of analytical results, but also by providing guidance regarding important features for analysis. ML teaches machines to identify and respond to patterns. Many traditional analytical methods are applied within ML algorithms, including Support Vector Machines, Bayesian, clustering analysis, and many others.

Common goals for ML are reducing data to key dimensions, and segmenting or clustering those dimensions according to the outcomes with which they are associated.

A classic problem with ML is separating causal signal from spurious correlations caused by statistical overfitting. ML algorithms often give a lot of statistically significant results that are eventually determined not to have any causal relationship to target outcomes.

Importantly, by combining ML with MR, it is possible to guide (supervise or train) ML analysis with existing MR ontologies. It is also possible to contextualize and test ML results. MR-enabled ontologies can detect and correct false patterns and generate new hypotheses. If new data that emerges from an ML analysis contradicts relationships defined by expert ontologies, either the new data is spurious, or a substantial new hypothesis is called for. If targeted research on causality bears out, the MR-enabling ontology may need to be updated. It is also possible to test ML results using more or less traditional methods by uploading to existing integrated databases or knowledge bases, to determine if the ML results align with what is currently understood about a particular molecule and biological mechanism.

**CONCLUSIONS – EFFECTIVE GENERAL AI COMBINES TRADITIONAL, MR & ML METHODS**

MR can be thought of as knowledge-based data intelligence, building on expert knowledge and flexible semantics. Most forms of MR require ontologies that describe expected data qualities and relationships in an area of interest. Computing with ontologies enables reasoning based on logic and assertion. In MR, computers are able to apply and identify patterns and create entailments and hypotheses.

Particularly when combined with traditional data quality methods, MR makes it possible to curate, enrich, and integrate large, messy, even incomplete datasets at lower time and cost. The examples provided in this article show how MR can help fill in the gaps in sparse datasets. MR can also combine with ML to make new discoveries possible with less wasted time and higher confidence.

ML can be thought of as analysis and supervision, or training-based data intelligence. ML commonly requires lots of clean data, including features and outcomes. ML also commonly requires training, based on training data (in which important features and outcomes are known) and supervised acceptance or rejection of results to guide the algorithm. ML teaches computers to identify potentially important variables and
patterns of combined variables through application of analytical methods, including Support Vector Machines, Bayesian, regression, visualization, decision trees/rules, random forests and many others.

ML is often more exploratory and potentially risky compared to MR. This article reviewed an example for application of ML that clusters potential drug compounds according to their performance on a multi-variable retrospective analysis of candidate compounds and target outcomes. Risks in using ML can be reduced substantially by combining ML with MR and traditional methods that help confirm or correct spurious results that are common to ML.

FOR SUCCESS WITH AI – AVOID OVERHYPED MOON SHOTS, ADDRESS PRACTICAL CHALLENGES

This short article has briefly reviewed the two main types of AI that are currently solving real-world problems in drug discovery. The possibilities are immense - by combining traditional data quality processes with advanced AI methods, computer science has only just begun solving basic time-consuming challenges that have plagued the industry for years. Specifically, blending traditional methods with advanced AI capabilities, such as ML and MR, can make it more cost-efficient to overcome basic research and business blockers, with higher quality results.

Scientists can avoid risk and ensure practical success by focusing more narrowly on specific applications that can solve tedious and costly problems, rather than by shooting for the moon with over-ambitious AI applications that impact core business models. AI can solve practical challenges in drug research – not only benefitting patients but also creating a new competitive landscape for drug developers. ♦

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BIOGRAPHY

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MULTIPARTICULATE FORMULATIONS

Using Multiparticulate Technology to Develop Pediatric Drug Products

By: Sven Stegemann, PhD, Matt Shaffer, Samantha Saville, Jaspreet Arora, PhD

INTRODUCTION

In 1969, the Supreme Court made it clear that drug products must serve public health and that the FDA’s role was to enforce this objective. More recently, the FDA and other regulatory bodies have presented new guidance for drug product development in serving special populations, such as pediatric patients, and will likely extend regulations for those populations through its latest initiative on “patient-focused drug product development.”

Currently, the Pediatric Research Equity Act (PREA) requires that all new chemical entities (excluding orphan designations) have pediatric-specific studies (where pediatric use is anticipated) assessing safety and efficacy, as well as pediatric-specific dosage forms as part of the approval process. PREA requirements are triggered by approval applications for new API as well as new indication, dosage form, dosing regimen, or route of administration. Additionally, the Best Pharmaceuticals for Children Act (BPCA) provides financial incentives for companies to voluntarily conduct pediatric studies for existing drug products.

This regulatory guidance has had a marked impact on new drug development pipelines and new drug approvals (NDAs). For the 10-year period from 2007-2017, the FDA approved 202 pediatric, small molecule prescription-bound new drug approvals, inclusive of both new marketing authorizations and new indications. Traditional tablet and liquid formats (liquids, solutions, and suspensions) accounted for the majority of these approvals. However, multiparticulate (MP) formulations accounted for 23 unique product approvals, and we expect this number to increase substantially in the future given MP format advantages over other technologies, including dosing flexibility, stability, safety, ease of administration, taste-masking, and tailored delivery to meet target product profiles.

As pediatric formulations are expected to continue as a core research area in pharmaceutical technology, MP technologies have the potential to play a key role. For pediatric and other specialized patient populations, in which the formulation and dosage form of the drug molecule plays an especially crucial part in achieving the best benefit-to-risk profile during treatment, multiparticulates’ flexibility help meet the combined challenges of specialized patient needs, drug requirements, and industrial and commercial viability.

DEFINING THE DRUG PRODUCT REQUIREMENTS

Today’s formulators have a variety of drug delivery systems to choose from when developing medicines for patients with special needs, such as pediatric, geriatric, or dysphagia patients. Selection of the best drug delivery system, however, requires an efficient, systematic approach that considers a drug’s physical and chemical properties and the targeted patient population’s requirements. Across all drug development processes, the starting point is defining the target product profile. Some general considerations for pediatric drug products are shown in Table 1.

Multiparticulates, which consist of multiple discrete drug-containing particles that together make up a single dose, are an emerging technology particularly well-suited for pediatric applications because they meet the majority of these considerations. Their advantages include tailored dissolution...
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profiles, safe swallowability and taste-masking, high dose flexibility and accuracy of administered dose, improved correlations between in vitro and in vivo test results, and suitability for a variety of dosage forms, including capsules, using standard pharmaceutical manufacturing. But most importantly, recent clinical studies have proven that multiparticulate forms are the most preferred and accepted dosage form among very young to young children.5,6

SELECTING THE APPROPRIATE MULTIPARTICULATE TECHNOLOGY

Multiparticulates can be called particles, pellets, mini tablets, microspheres, granules, and beadlets and are made using processes including melt-spray congealing (MSC), extrusion-spheronization, tableting, and fluid-bed coating. For pediatric patients, multiparticulates are mainly administered through sprinkling them on 5- to 15-ml portions of child-preferred soft food, an approach that is endorsed by FDA guidance.7

The four main multiparticulate technology approaches used for drug delivery in pediatric patients — lipid multiparticulates (LMPs), spray-layered dispersions, pellets, and mini tablets — are differentiated by their manufacturing processes, achievable particle sizes, and typical drug loadings. As Figure 1 shows, each of these delivery options is based on unit operations used in conventional pharmaceutical manufacturing, lending maximum flexibility to technology selection.

The four main multiparticulate technology approaches used for drug delivery in pediatric patients — lipid multiparticulates (LMPs), spray-layered dispersions, pellets, and mini tablets — are differentiated by their manufacturing processes, achievable particle sizes, and typical drug loadings. As Figure 1 shows, each of these delivery options is based on unit operations used in conventional pharmaceutical manufacturing, lending maximum flexibility to technology selection.

Selection of the most appropriate multiparticulate dosage form follows a four-step process, including: (1) a clear definition of the target product profile that includes patient needs; (2) assessment of the compound’s physical/chemical properties and selection of the multiparticulate technology approach; (3) optional addition of a functional and/or cosmetic coating; and (4) preparation of the ultimate dosage form and packaging.

Selection from these options derives from the desired drug form and release target, according to therapeutic needs. In some cases, developers can use the crystalline form of the drug as supplied, while in others a solubility-enhanced or amorphous form may be required. Depending on the desired delivery, an immediate-release product or modified-release characteristic may be preferable. Other attributes come into play in determining the right multiparticulate technology for the product, including (1) an achievable pharmacokinetic profile, (2) selection from these options derives from the desired drug form and release target, according to therapeutic needs. In some cases, developers can use the crystalline form of the drug as supplied, while in others a solubility-enhanced or amorphous form may be required. Depending on the desired delivery, an immediate-release product or modified-release characteristic may be preferable. Other attributes come into play in determining the right multiparticulate technology for the product, including (1) an achievable pharmacokinetic profile, (2)...

### TABLE 1

<table>
<thead>
<tr>
<th>Formulation targets of end users</th>
<th>Formulation targets of suppliers</th>
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<tr>
<td>• Therapeutic needs</td>
<td>• Physical requirements</td>
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<tr>
<td>• Dose strength availability</td>
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<td>• Dose accuracy</td>
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<td>• Dose titration/adjustment</td>
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<td>• Excipient safety &amp; burden</td>
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<td>• Pediatric patient and caregiver needs</td>
<td>• Standard processing</td>
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<td>• Swallowability</td>
<td>• Ambient storage conditions</td>
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<td>• Palatability</td>
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<tr>
<td>• Taste</td>
<td>• Reproducibility of quality</td>
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<tr>
<td>• Swallowed dose accuracy</td>
<td>• Ease of global transport</td>
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<tr>
<td>• Administration-ability</td>
<td>• Shelf-life &gt; 2 years</td>
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<tr>
<td>• Dosage form usability</td>
<td>• Cost of goods</td>
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<td></td>
<td>• Global supply chain</td>
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Selected general considerations for the development of pediatric formulation

### FIGURE 1

Primary multiparticulate technologies with common design attributes
a reliable and stable formulation, and (3) reproducible and scalable manufacturing processes. Those considerations, in addition to incorporating the physical and chemical characteristics of the drug molecule – including its size, solubility, dissolution rate, excipient compatibility, and chemical stability – determine a best-choice technology approach for the drug-containing multiparticulate core.

Independent of the technology chosen, functional coatings may be considered to improve product flow or handling, to improve taste-masking, or to further modify the drug-release profile. Examples of coating types include extended release for metering the dose over time, and pH-targeted release or time-targeted release for taste concealment or gastric protection. Coatings do increase the complexity of the formulation and processes.

The selection of the dosage form is a final consideration in developing multiparticulate formulations that match the needs of patients, caregivers, and the industry. Dosage form options include orally disintegrating tablets (ODTs), suspensions, sachets, and sprinkle capsules, comprising a variety of choices for formulators. Moreover, recent innovations in drug-device combinations give more options for presenting both microspheres and mini tablets to patients. Whether a traditional dosage form or a device is selected, the best practice is to evaluate several criteria, including usability, ability for dose adjustment, available technology, cost of goods, stability, and product robustness.

Figure 2 demonstrates the methodology for identifying a product concept to test in the clinic. The approach begins with a decision on the most appropriate technology to accommodate the design attributes based on the patient needs, drug properties, and target product profile (TPP). This is followed by a pragmatic approach to the development of a formulation – one that identifies potential product risks at each step, yet informs a data-driven final decision to be made for progressing the formulation to be studied in human trials.

CASE STUDY: DEVELOPING A PEDIATRIC FORMULATION OF ACETAZOLAMIDE USING LIPID MULTIPARTICULATE (LMP) TECHNOLOGY

FDA guidance on pediatric drug products emphasizes design that promotes safety, accurate dosing, and enhanced acceptability.\(^8,9\) Multiparticulates inherently possess these attributes, making them a well-suited technology platform for pediatric dosage forms.

Presented below is a case study for developing a pediatric formulation of an extended-release product containing the active pharmaceutical ingredient (API) acetazolamide, which is currently available for prescription to adults in the form of a 500-mg capsule. The example outlines selecting lipid multiparticulate technology for the product; jet milling to reduce the API particle size; determining formulation bounds via melt-screening; developing a formulation design space to achieve the desired release rate;
manufacturing prototypes and conducting stability testing; and finally nominating final formulations for clinical testing against an existing acetazolamide product.

Acetazolamide is a weakly acidic crystalline form with a melt point over 200°C and is considered very slightly water soluble. It is a carbonic anhydrase inhibitor and most commonly known for the treatment of glaucoma. The age-appropriate acetazolamide formulation is sought to accommodate children between 6 months to 12 years of age, and requires an oral dose range of 50 to 500 mg. The initial design target was to achieve 80% of the dose released over 12 hours in an in vitro test as a formulation suitable for an early clinical study to test the relative bioavailability of the product in adults. Subsequently, these data could be used to establish models to guide the clinical design for pediatric patients. The requirements for the formulation were to demonstrate delivery of the intended dose, tunable release, and phase-appropriate stability. This was accomplished using material-sparing formulation development approach for the specific technology and accelerated stability conditions to inform formulation stability beyond the clinical timeline.

Lipid multiparticulates (LMP) technology was chosen for particle size, narrow distribution, high degree of sphericity with smooth surfaces; promoting palatability, good flow, and easy handling. An accurate dose is delivered by weight, inclusive of thousands of discreet LMPs, allowing multiple doses to be administered with the same formulation. Multiple final dosage forms are also possible when using this technology and can be explored in future clinical studies. By supplying the formulation in bulk for early phases in the clinical trial, flexibility can be maintained for ascending doses and body mass or surface area dose adjustments.

Under a self-imposed constraint of limited API, the formulation design approach for early clinical studies produced small batch sizes on a commercially relevant atomizer at similar flow rates. With the reduction of available materials, the characterization techniques also needed to be modified and scaled down to accommodate initial and stability testing. Because the size distribution of the API had a significant fraction greater than 100 microns, there was a risk of drug dissolution rate impacting release and content uniformity in the 200 micron microspheres. A jet mill was used to reduce the majority of the drug particles to below 20 microns. Two excipients were selected for screening based on release rate models developed by past formulation experiments (DOE) having three levels and two factors, with drug dissolution being the primary output. The two factors within the formulation were the drug content and the poloxamer fraction of the total excipients in the formulation. The drug content levels were 10%, 25%, and 40%, bracketing intended fill masses of 125 to 500 mg for the lowest dose. The poloxamer fractions were 2%, 4%, and 6%, in an attempt to center the design space on the release target for the drug solubility. The excipient burden bracketed by this study would be 75 to 4200 mg/dose for glyceryl behenate and 4.5 to 340 mg/dose for poloxamer 407. Furthermore, the study design would also be informative on the compatibility of the drug with the two excipients for processing and storage stability using the secondary output of organic impurities. At the extremes, the ratios of poloxamer to drug ranges from 0.08 to 0.67, and for glyceryl behenate...
to drug from 1.5 to 8.5.

Five different prototypes were manufactured using less than 50 grams of total API with 67% to 86% product yields in batch sizes of less than 30 grams. The atomizer was adjusted based on melt viscosity resulting in spherical particles with a median size of 220 to 270 microns for all compositions. Prototypes were annealed for 7 days at 50°C/75%RH, then tested for dissolution performance using a paddle apparatus scale to a reduced volume of 100 mL. The dissolution performance was based on the two formulation factors as shown in Figure 3 with the actual percentage release at 12 hours in parentheses. The results show the actual design space had more of an extended release than originally predicted from the drug solubility.

Prototypes CR-2 and CR-5 were chosen for stability evaluation at 25°C/60%RH and 40°C/75%RH for 6 months in the open configuration in HDPE bottles. These aggressive storage conditions provide stability data regarding drug dissolution, potency, and purity toward the product’s predicted two-year shelf-life. CR-2 had achieved the dissolution performance target initially and had the highest excipient ratios of the design space. CR-5 demonstrated a differentiated release rate, more appropriate drug loading for dosage form flexibility and the highest overall poloxamer content of the design space.

For the accelerated storage condition, CR-2 met the characteristic of 65% to 85% release at 12 hours and CR-5 25% to 55% release. The potency of both formulations met 90% to 110% of the label claim. Drug purity was maintained at 99.8% to 99.9% with no related organic impurity greater than the limit of quantitation (LOQ) of 0.05%.

Two compositions were recommended as clinical formulation for the bioequivalence comparison with the adult product. CR-2 met the target requirements to be one of the recommended compositions. The second formulation recommendation can come from a pharmacokinetic model informing the expected in vivo behavior of these particles compared to the adult capsule. If the LMP delivery is expected to be faster than capsule, one could interpolate the formulation space to select a slower-releasing composition. For example, a composition with 20% drug and a 5% poloxamer fraction would result in slower-releasing particles. If the contrast is true and a faster releasing composition is needed, a second formulation could be extrapolated to achieve 80% release in 6 hours. Given the uncertainty of the model, the preferred approach in this case would be a demonstration prototype or a further built-out design space.

In this case study, the LMP technology approach provides a consistent delivery mechanism with tunable drug release by varying the pore former content. A stable, solid oral product concept was demonstrated with recommendations for clinical prototypes, using knowledge of the formulation space to inform key performance and stability attributes. During scale-up, the LMP technology can maintain atomization parameters, controlling key performance attributes of particle size and content uniformity, and therefore facilitate rapid progression to late clinical and commercial stages. The flexibility to administer multiple accurate doses with multiple final dosage options allows for customization of the final product based on patient needs. The LMP
technology provides an age-appropriate formulation design to be tested in a clinical study to first establish safety and is appropriate for quick translation for dosing into the pediatric patient population.

SUMMARY

With guidance and incentives from regulatory authorities, the development and provision of pediatric dosage forms have become an important field in drug delivery. The rise of patient-centric drug product development, along with increasing personalization of drug therapies, requires more flexible industrial manufacturing platforms and new drug development frameworks – to give patients with special needs access to the medicines they urgently require. Multiparticulate technologies have improved throughout the past 40 years and continue to be a source of innovation due to their flexibility in leveraging large-scale, high-throughput bulk manufacturing advantages, coupled with standard capsule filling, to provide a broad range of metered dose strengths that cover neonates through to adolescence. The case study shows the flexibility of lipid multiparticulate technology in modifying drug release for desired clinical target.

Considering the emerging patient demand and regulations for patient-centric drug product design, multiparticulates have the potential for use across all age groups and specific disease populations requiring dose flexibility and ease of oral administration.

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Ultra-small particles hold unique properties and represent an emerging area of investigation for biomedical applications. These ultra-small particles are able to fill the gap between single molecules and conventional larger-size nanoparticles in terms of their spatial dimensions, as well as their physicochemical and pharmacokinetic (PK) properties. In contrast to regular nanoparticles used in medical applications, such as liposomes or block copolymer micelles with sizes larger than 10 nm, ultra-small particles with sizes below the glomerular filtration cut-off are able to clear the body efficiently via the urinary system, reducing the risk of adverse events. Additionally, as a result of the faster diffusion of small objects relative to larger ones, ultra-small particles can effectively penetrate solid tumors and the surrounding tumor microenvironment, both of great importance for efficient drug delivery. At the same time, ultra-small particles exhibit increased surface area-to-volume ratios as compared with those for larger-size particles, leading to relatively high drug-loading capacities and ligand numbers.

**FIGURE 1**

Comparison of C-Dot & Serum Protein

Molecular renderings of serum albumin protein (left) and C-Dot (right). Part of the C-Dot rendering is removed to show the interior. In the molecular renderings, silicon, oxygen, carbon, hydrogen, nitrogen, and sulfur atoms are color coded in purple, red, gray, white, blue, and yellow, respectively.
A FIRST-IN-CLASS ULTRA-SMALL PARTICLE PLATFORM FOR FIGHTING CANCER

Elucida Oncology™ is focused on transforming outcomes for patients harboring primary solid tumors or metastatic disease. The company was founded in 2016 with the goal of personalized cancer care using an ultra-small hybrid silica particle, C-Dots (Figure 1), for image-guided surgical treatment or for delivery of a variety of therapies to improve patient outcomes. The C-Dot structure serves as a treatment transport unit, and is uniquely designed to accurately deliver diagnostic, imaging, and therapeutic agents to cancer cells, or to safely clear the body through the kidneys.

C-Dots share many similarities with proteins, e.g., with respect to size and surface properties, but contain amorphous silica as a core scaffold (Figure 1). In fact, silica is one of the major biogenic materials, and it widely exists in plants and animals, such as grasses and marine microbes. While natural proteins are constructed from linear chains of amino acids (Figure 1), C-Dots are assembled on the basis of a three-dimensional (3D) crosslinked silica network as the core, onto which biocompatible polymers and functional peptides, drugs, and contrast labels are covalently attached (Figure 1). Based on the rich library of silica forming alkoxy silane compounds, silica chemistry can be adopted to precisely manipulate particle architecture and properties, rendering C-Dots a powerful platform with highly engineered functions for biomedical and clinical applications, and constituting organic-inorganic hybrid protein mimics.1

UNIQUE PARTICLE DESIGN EVOLUTION

This silica-based biomaterial platform was originally invented by Prof. Ulrich Wiesner at Cornell University in 2005.2 The first-generation larger-size (~30 nm hydrodynamic diameter) fluorescent core-shell silica particles synthesized in alcohol solutions covalently encapsulated fluorescent dyes within its core. The rigid silica shell surrounding these dyes led to a significant increase in per dye fluorescence brightness. Since several dye molecules were simultaneously encapsulated inside a single particle without significant detectable energy transfer between them, the overall fluorescence brightness of the particles was very high when compared to a regular fluorescent dye.3 In 2009, the Wiesner group reported on the development of the first silica particles with sizes

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**FIGURE 2**

Molecular renderings of penta-functional C-Dot. The five functions include fluorescence from encapsulated near-infrared (NIR) dyes, cancer targeting by specific peptides, delivery of chemotherapy by attachment of a small drug via cleavable linker groups, radioisotope labeling via specific chelators, and pH sensing by employing silica surface attached sensor dyes. Silicon, oxygen, carbon, nitrogen, sulfur, chlorine, and fluorine atoms are color coded in purple, red, gray, blue, yellow, green, and light green, respectively. Hydrogen atoms are not displayed for better visualization.
below 10 nm, and sterically stabilized with a surface layer of poly(ethylene glycol) (PEG).4,5 As part of a first collaborative effort with Prof. Michelle Bradbury at Memorial Sloan Kettering Cancer Center (MSK), these sub-10 nm PEGylated silica particles were demonstrated to rapidly clear through the kidneys after murine tail vein injection.6 The team subsequently attached cyclic arginine-glycine-aspartic acid (cRGD) cancer-targeting peptides to the end of some of the PEG chains on the particle surface to target surface integrin receptors.7 In vivo studies in small animal tumor models demonstrated a favorable safety profile and high tumor targeting efficacy of these sub-10 nm integrin-targeted silica particles, leading to Food and Drug Administration (FDA) investigational new drug (IND) approval for a Phase 1 first-in-human clinical trial using C-Dots in 2011.8

Since then, a new generation of C-Dots has been developed, now synthesized in aqueous instead of alcohol solutions using a highly efficient chemical approach.9,11 This versatile synthesis allows the silica core of C-Dots to be precisely engineered at the single atomic layer level, with the PEGylation step integrated into a one-pot type batch reaction. C-Dots (Figure 2) can encapsulate a variety of spectrally distinct dyes exhibiting different absorption/emission characteristics in the visible to near-infrared range, yielding an ultrabright particle with exquisitely high detection sensitivity and fluorescence-based multiplexing capabilities for clinical cancer care. Multiple cancer-targeting peptides are attached to the end of some of the PEG chains, endowing C-Dots with multi-valency enhancement to increase potency and cellular binding affinity. Radioisotopes can be attached onto the silica surface, enabling, e.g., positron emission tomography (PET) imaging or radiotherapy. Furthermore, a large number of small molecule drugs can be simultaneously “clicked onto” additional functional groups of the organic C-Dot shell for drug delivery applications.12,13 Inserting a number of these functional groups does not influence the favorable biodistribution and PK profiles observed for C-Dots. Figure 2 shows an example in which a total of five functions were integrated in a single C-Dot, i.e., fluorescence, cancer-targeting, pH-sensing, radioisotope chelating, and drug delivery, while the overall C-Dot size remained around 7 nm, thereby providing a particle with both diagnostic and therapeutc features, i.e., a particle for theranostics.11
C-DOT DIFFERENTIATORS

There are several advantages of the C-Dot platform that differentiate it from other particles used in cancer theranostics that could have a profound impact on the dose-limiting toxicity associated with current cancer drugs. First, the size of C-Dots is ultra-small and can be precisely tuned to sub-10 nm sizes with less than 1 nm accuracy, important for achieving efficient renal clearance and extended circulation lifetimes. Second, the surface properties of C-Dots are engineered by a novel PEGylation mechanism, which facilitates further surface modifications. This specific reaction mechanism increases their colloidal stability in blood serum. As a result, and unlike other nanoparticles that adsorb proteins onto their surface, a protein corona does not form around the C-Dot surface under physiological conditions. This prevents C-Dots from being identified by the mononuclear phagocytic system (MPS) and helps achieve desirable biodistribution profiles. Third, a single 7 nm C-Dot can integrate up to five surface functionalities without exceeding the threshold for renal clearance, a characteristic not demonstrated by any other platform.

Interestingly, it has been found that the PK profiles of C-Dots do not significantly change in the presence of functional ligands having different molar masses and chemical properties. These properties have endowed C-Dots with distinctive PK profiles, as well as high cancer-targeting efficiencies. C-Dots are renally cleared after intravenous injection in both preclinical models and human subjects. At the same time, C-Dot surface functionalization with a variety of targeting moieties, has shown high targeted delivery and uptake (up to 17% ID/g for anti-HER2 scFv fragments) and target-to-background ratios (>20 at 10 days post-injection). It is substantially higher than that typically found for larger nanoparticle platforms. More importantly, the remaining C-Dots that do not end up in tumors are rapidly cleared from the body without substantial off-target effect. This “target-or-clear” property of C-Dots highlights the enormous potential of this platform for a variety of nanomedicine applications (Figure 3).

APPLICATIONS IN CANCER DIAGNOSIS & TREATMENT

This versatile platform enables the development of a family of C-Dots that are adapted with different targeting moieties, contrast labels, and/or therapies, some of which are in active clinical trials at MSK for image-guided cancer treatment of primary/metastatic disease. For example, C-Dots, in which near-infrared fluorescent dyes are encapsulated inside the core and which bear cancer-targeting peptides on the surface, are currently being used for image-guided surgery in a Phase 2b clinical trial. These ultrabright near-infrared fluorescent C-Dots can light up cancerous lymph nodes, and aid in their surgical removal using real-time fluorescence imaging guidance. In addition, targeted C-Dots can be modified for multi-modality (PET-optical) imaging, enabling them to both detect and treat cancer via PET-optical imaging and radiotherapy. Interestingly, C-Dots are also able to kill cancer cells without using a cytotoxic drug. In nutrient-deprived cancer cells, C-Dots can trigger a special non-apoptotic cell death mechanism, i.e., ferroptosis, which sets itself apart from mechanisms observed for other conventional particle platforms. Importantly, healthy tissues in the same animal are not adversely affected. This constellation of unique interactions that selectively trigger specific cell death pathways in cancer cells and surrounding environment further sets C-Dots apart from the classic nanoparticles, rendering them more like protein mimics.

THE POTENTIAL TO TRANSFORM CLINICAL PRACTICE

Elucida Oncology, together with MSK and Cornell University, are now focusing on the further development and the commercialization of C-Dots for clinical cancer care. We expect C-Dots, by overcoming the suboptimal pharmacokinetic properties typically found with larger particle probes and antibodies, will be able to significantly improve targeted detection and treatment of disease while eliminating dose-limiting toxicity, in turn, transforming clinical practice.

It took the research team more than a decade to bring C-Dots from the original lab reaction batch to the current state with multiple ongoing clinical trials. In addition to the authors, a significant number of individuals have made substantial contribu-
tions to the development of this particle platform. In particular, the authors acknowledge the contributions of Alexander Andrievsky, Prof. Barbara Baird, Dr. Daniel Bonner, Dr. Andrew Burns, Ying Cong, Nikhil Dhawan, Jennifer Drewes, Tom Gardiner, Dr. Erik Herz, Josh Hinckley, Dr. Teresa Kao, Dr. Ferdinand Kohle, Dr. Daniel Larson, Songying Li, Carlie Mendoza, Dr. Hooisweng Ow, Dr. Teeaporn Suteewong, Melik Turker, Prof. Watt Webb, and Dhuan Zang from Cornell University. Contributors on the MSK side included Dr. Cameron Brennan, Dr. Sarah Cheal, Dr. Feng Chen, Dr. Nick Chen, Dr. Elisa DeStanchina, Dr. Hedvig Hricak, Dr. John Humm, Dr. Rupa Juthani, Dr. Daniella Karassawa, Dr. Sung Eun Kim, Dr. Steven Larson, Dr. Jason Lewis, Dr. Serge Lyaschenko, Dr. Brian Madajewski, Dr. Michael McDevitt, Dr. Lee MacDonald, Dr. Ingo Mellinghoff, Dr. Larry Norton, Dr. Michael Overholtzer, Dr. Snehal Patel, Dr. Oula Penate-Medina, Dr. Evan Phillips, Dr. Charles Rudin, Dr. Peter Scardino, Dr. Howard Scher, Dr. Sonia Sequeira, Dr. Hilda Stambuk, Dr. Jedd Wolchok, Dr. Barney Yoo, Dr. Robert Young, Dr. Pat B. Zanzonico, and Dr. Li Zhang. We also would like to acknowledge contributions of Dr. Fabio Gallazzi, Prof. Thomas Quinn, and Dr. Xiuli Zhang from the University of Missouri.

REFERENCES


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