Drug Development & Delivery

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Oral Thin Films: An Emerging Delivery System

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

Ronald Aung-Din, MD
NeuroDirect Effects CBD: Non-Systemic Cannabidiol for Autism Spectrum Disorder

Cindy Dubin
Excipients: Matching Ingredients to Molecules Improves Functionality

Jane Reed, PhD
How Life Sciences Companies Are Leveraging NLP From Molecule to Market

IN THIS ISSUE

INTERVIEW WITH TEDOR PHARMA'S PRESIDENT & CEO **DOUG DRYSDALE**

GATTEFOSSÉ

Melt Extrusion

Compritol® | Precirol® | Gelucire®

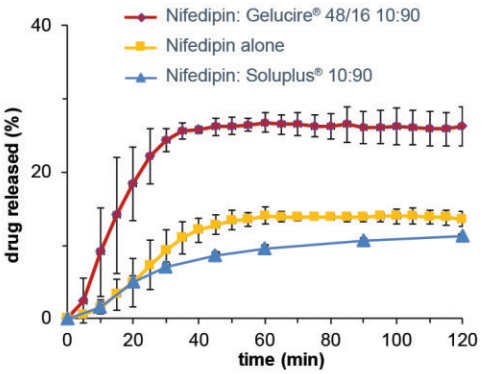
Solid Dispersions with Lipids

Solvent-free solid dispersions are possible with powdered glycerides like Compritol® and Precirol® or self-emulsifying polyoxylglycerides, e.g. Gelucire® 44/14 and 48/16. Whereas glycerides provide sustained release and taste masking, polyoxylglycerides are suitable for delivery of poorly soluble compounds.

Mild Processing Conditions

Solid dispersions for capsule filling or compression into tablets may be obtained by high shear granulation or hot melt extrusion. This is possible without use of any solvents and at temperatures near the excipient melting points, being 44°C to 72°C.

Depending on the choice of excipient and process, these excipients may serve as plasticizers, and carriers for a wide range of API.



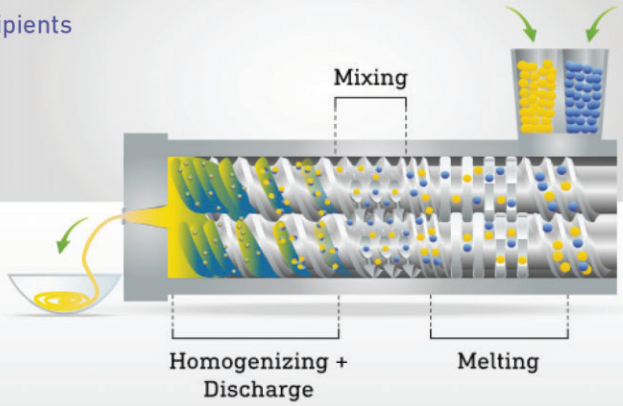
Drug release from Nifedipine milled extrudates filled into hard gelatin capsules

Contact Us

We help clients in various stages of drug development, beginning with drug solubility screening in solid lipid excipients, evaluating stability and compatibility with the API, and the characterization of the drug delivery system.

Melt extrusion with lipid excipients

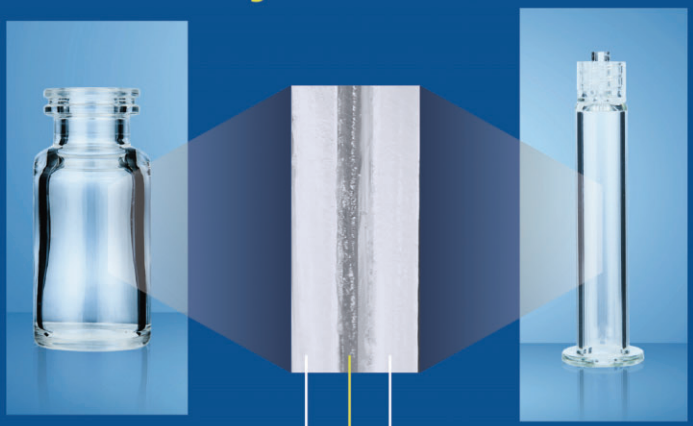
Gelucire® 48/16
Extrudate



gattefosse.com/hot-melt-extrusion

OXYCAPT™ Plastic Vial & Syringe

Multilayer Structure



Water Vapor Barrier Layer (COP)

Oxygen Barrier Layer (New Polymer)

Drug Contact Layer (COP)

- Excellent Oxygen Barrier
- High Water Vapor Barrier
- Very Low Extractables
- Low Protein Adsorption
- Excellent Ultraviolet Barrier
- High Break Resistance
- High pH Stability
- Silicone Oil Free Barrel
- Gamma-sterilized Vial & Syringe
- Customizable
- For Biologics & Regenerative Medicine

MITSUBISHI GAS CHEMICAL

Mitsubishi Gas Chemical Company,Inc.

https://www.mgc.co.jp/eng/products/abd/oxycapt.html

Mitsubishi Gas Chemical America, Inc.

http://www.mgc-a.com

E-mail: nb3.pharmapackage@mgc.co.jp

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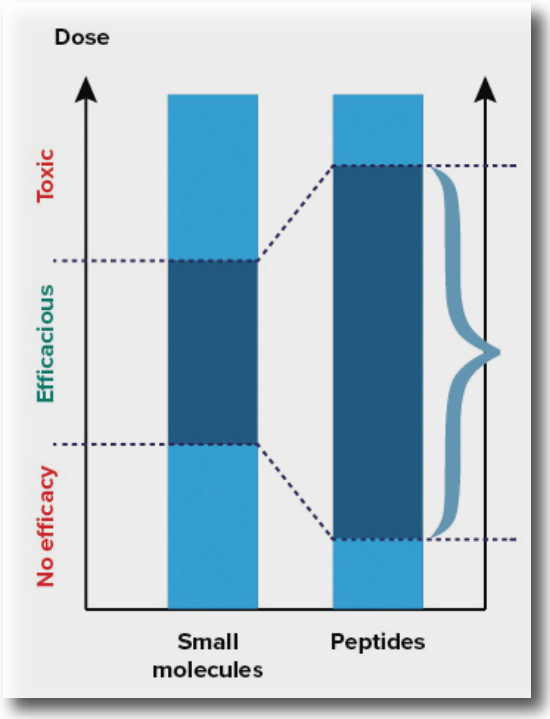
Therapeutic Peptides

"The high-quality, high-process consistency between manufacturing runs and the in-line PAT analytics of the µLOT platform will enable unprecedented robustness of the manufacturing process, significantly retiring the risk of failure to supply due to non-scalability of the manufacturing process. Furthermore, in case of process mishaps, the ribbon tracking system will allow the µLOT users to identify exactly what part of the ribbon is out of specification and discard this and in this way, rescuing the rest of the production."



p.28

Table of Contents

Cambrex

Your molecule
Our mission

Drug substance | Drug product | Analytical services

www.cambrex.com

Matching Ingredients to Molecules

"The pharmaceutical excipients market is projected to reach $9.7 billion by 2025, up from $6.9 billion in 2019. Industry experts point to advancements in functional excipients, the emergence of multifunctional excipients, and co-processed excipients, as well as an increase in biopharmaceuticals and the rising adoption of orphan drugs as the reasons behind this expected growth."

p.45

Departments

Table of Contents

abbvie

CONTRACT MANUFACTURING

Biologics | ADCs | Potent | Drug Product | Fermentation
Fill/Finish | Hot Melt Extrusion | APIs

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Experience Unrivaled

Contract Manufacturing

When it comes to outsourcing focused on commercial success, you need a CMO that has been there many times through deep scientific expertise and world-class facilities.

Pfizer & BioNTech to Co-develop Potential COVID-19 Vaccine

Pfizer Inc. and BioNTech SE recently announced the companies have agreed to a letter of intent regarding the co-development and distribution (excluding China) of a potential mRNA-based coronavirus vaccine aimed at preventing COVID-19 infection. The companies have executed a Material Transfer and Collaboration Agreement to enable the parties to immediately start working together.

The collaboration aims to accelerate development of BioNTech's potential first-in-class COVID-19 mRNA vaccine program, BNT162, which is expected to enter clinical testing by the end of April 2020. The rapid advancement of this collaboration builds on the research and development collaboration into which Pfizer and BioNTech entered in 2018 to develop mRNA-based vaccines for prevention of influenza.

"We are proud that our ongoing, successful relationship with BioNTech gives our companies the resiliency to mobilize our collective resources with extraordinary speed in the face of this worldwide challenge," said Mikael Dolsten, Chief Scientific Officer and President, Worldwide Research, Development & Medical, Pfizer. "We believe that by pairing Pfizer's development, regulatory and commercial capabilities with BioNTech's mRNA vaccine technology and expertise as one of the industry leaders, we are reinforcing our commitment to do everything we can to combat this escalating pandemic, as quickly as possible."

"This is a global pandemic, which requires a global effort. In joining forces with our partner Pfizer, we believe we can accelerate our effort to bring a COVID-19 vaccine to people around the world who need it," said Ugur Sahin, Co-Founder and CEO of BioNTech.

The companies expect to utilize multiple research and development sites from both companies, including in the United States and Germany, to house the activities identified by the collaboration agreement.

The companies will begin collaborating immediately. They will finalize details of the agreement regarding financial terms, and all activities related to development, manufacturing and potential commercialization over the next few weeks.

On March 13, 2020, Pfizer issued a five-point plan calling on the biopharmaceutical industry to join the company in committing to unprecedented collaboration to combat COVID-19.

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world.

Exagen Inc. Partners With Sonora Quest Laboratories to Offer AVISE Testing for Patients Suspected of Autoimmune Disease

Exagen Inc. recently announced it has entered into a strategic partnership with Sonora Quest, the nation's largest integrated laboratory system. The agreement provides preferred access through Sonora Quest in Arizona to Exagen's AVISE testing. The testing can facilitate improved care through the differential diagnosis, prognosis, monitoring and therapeutic optimization of complex and incurable autoimmune rheumatic diseases. The details of the agreement are confidential.

"We're pleased to be working with Sonora Quest in a shared commitment to improve patients' lives. Expanding access to our portfolio of innovative products will have a significant impact on patients, enabling rheumatologists to improve patient care through insights available exclusively through our patented technology," said Ron Rocca, President and CEO of Exagen. "This is an important step towards helping the estimated 23 million Americans who are yet to be accurately diagnosed for conditions that can present with symptoms similar to lupus or rheumatoid arthritis."

"The AVISE tests add tremendous value to our continually expanding menu of testing, providing consumers in Arizona more power to proactively manage their health through access to innovative testing platforms," said Christina Noble, Chief Growth Officer at Sonora Quest Laboratories. "Lupus is known for being difficult to diagnose because its symptoms differ from person to person, mimic the symptoms of many other diseases, and can come and go. A Lupus Foundation of America survey found that on average, it takes nearly six years for people with lupus to be diagnosed, and this partnership seeks to reduce that delay."

AVISE testing will be available through healthcare provider customers of Sonora Quest beginning in spring 2020. Healthcare providers and patients and their families can find more information about this testing at www.avisetest.com and can expect to see additional information on www.SonoraQuest.com in the coming weeks.

Autoimmune rheumatic diseases are a diverse group of conditions that primarily impact the joints, bones, muscle and connective tissue. Patients with these autoimmune diseases often suffer debilitating symptoms such as pain, depression and fatigue leading to reduced quality of life and loss of productivity. Diagnosing these conditions early is difficult and there is no known cause nor cure. Women are disproportionately affected by autoimmune rheumatic diseases and in lupus, for example, more than 85 percent of patients are female.

Exagen is dedicated to transforming the care continuum for patients suffering from debilitating and chronic autoimmune diseases by enabling timely differential diagnosis and optimizing therapeutic intervention. Exagen has developed and is commercializing a portfolio of innovative testing products under its AVISE brand, several of which are based on its proprietary Cell-Bound Complement Activation Products (CB-CAPs) technology. Exagen's goal is to enable rheumatologists to improve care for patients through the differential diagnosis, prognosis and monitoring of complex autoimmune and autoimmune-related diseases, including SLE and rheumatoid arthritis.

Evonik Achieves Major Biotech Breakthrough With a New Animal-Free & Fermentation-Based Collagen Platform

Evonik recently announced the development of an advanced collagen platform that is made via fermentation-based processes and devoid of animal- or human-derived materials. The recombinant technology will, for the first time, provide medical, pharmaceutical, cell culture, and tissue engineering markets with a highly soluble, ultra-pure form of collagen that is safe, sustainable, and commercially scalable.

Evonik's proprietary collagen platform features a triple helix structure and other biological properties that mimic many of the attributes of natural collagen so it can reliably interact with cells and tissues and be readily absorbed or remodeled by the body.

Animal-sourced collagen, currently the main source of collagen for use in life sciences, can be associated with batch-to-batch variability, potential transmission of diseases or pathogens, adverse immunogenic or allergic reactions, and non-sustainable sourcing methods. Evonik's collagen is produced under controlled conditions via a fermentation-based process. In addition to being sustainable and suitable for vegan use, this process delivers an ultra-high level of purity that is easily reproducible at any commercial scale.

"This is arguably our biggest innovation breakthrough in recent years: a fermentation-based collagen platform that can effectively substitute the use of animal-derived collagen in pharmaceutical, medical, and cell culture markets," said Dr. Thomas Riermeier, SVP and General Manager for the Health Care business line of Evonik. "We look forward to working with customers to develop the next-generation collagen products with an improved safety profile."

Evonik will utilize its established fermentation process technologies and global manufacturing network to commercialize the collagen platform for worldwide use. The company's application, formulation, and manufacturing competencies will also be used to help customers develop and commercialize their own biofabricated products.

The new collagen platform will also support Evonik's Tissue Engineering Project House, which was launched in Singapore in 2018 by the company's strategic innovation unit Creavis, to develop advanced biomaterial solutions in regenerative medicine.

Collagen is the main structural protein family in the body, contributing between a quarter and one third of total protein mass in humans and other mammals. It is important in the formation and functionality of body parts, such as skin, tissue, cartilage, organs, bone, bone marrow, cell membranes, ligaments, and hair. It is commonly used as a biomaterial in healthcare due to its biocompatibility, degradability, and structural properties that enable cell and tissue interaction. Product application areas include orthopedics, cardiovascular, wound care, ocular care, general surgery, dental care, drug delivery, and regenerative medicine. Virtually all medical and pharmaceutical-grade collagen used today is derived from animal-based sources.

Tyligand Bioscience & Context Therapeutics Sign Strategic Development Agreement for Onapristone ER

Tyligand Bioscience, Ltd., a leader in small molecule drug discovery and development, and Context Therapeutics LLC, a clinical stage biopharmaceutical company focused on hormone driven cancers, recently announced the signing of collaboration agreements for the development, manufacturing, registration and future commercialization of onapristone extended release (ER).

Onapristone ER is currently being evaluated in patients with progesterone receptor positive (PR+) ovarian and endometrial cancers in the ongoing Phase 2 ONWARD 220 clinical trial. Initiation of additional Phase 2 clinical trials in ER+, PR+, HER2- breast cancer and endometrial cancers are planned for mid-2020.

Under the terms of the agreements, Tyligand will be solely responsible for the design and optimization of a novel manufacturing process for onapristone ER to meet Context's development and future commercialization needs, and standards for quality, safety and cost. Upon completion of specific performance-based milestones, Tyligand will be granted the exclusive right and will be solely responsible for the development and commercialization of onapristone ER in China, Hong Kong and Macau (the "Territory"), and Context will be eligible to receive royalties on net sales of onapristone ER in the Territory. Context will retain rest of world rights to commercialize onapristone ER.

"We are thrilled to partner with Tyligand as we accelerate onapristone ER's Phase 2 evaluation and prepare for Phase 3," said Martin Lehr, CEO of Context. "Tyligand is renowned for its expertise in process development and has strong networks with manufacturing and clinical capabilities in China and the U.S. Partnering with Tyligand will enable Context to optimize and efficiently scale our manufacturing and clinical capacity to support the evaluation and future commercialization of onapristone ER, our experimental oral therapy, to address the unmet need in treating patients with PR+ cancers."

"Even with the major advances in cancer therapies in recent years, treatment options for patients with hormone driven cancers remain limited," said Tony Zhang, CEO of Tyligand. "Onapristone ER has the potential to be the first-in-class therapeutic agent specifically targeting progesterone receptors and the best-in-class treatment option for breast, endometrial and ovarian cancers. We are proud to partner with Context to develop onapristone ER and make this innovative medicine ultimately more accessible for patients around the world."

Onapristone ER (extended release) is a potent and specific antagonist of the progesterone receptor that is orally administered. Currently, there are no approved therapies that selectively target progesterone receptor positive (PR+) cancers. Preclinical and clinical data suggest that onapristone ER has anticancer activity by inhibiting progesterone receptor binding to chromatin, downregulating cancer stem cell mobilization and blocking immune evasion. Onapristone ER is currently being evaluated in patients with PR+ rare ovarian and endometrial cancers in the ongoing Phase 2 ONWARD 220 clinical trial. Additional Phase 2 clinical trials in ER+, PR+, HER2- breast cancer and endometrial cancers will be initiated in 2020. Onapristone ER is an investigational drug that has not been approved for marketing by any regulatory authority.

Nurix Therapeutics Closes $120-Million Financing to Advance Targeted Protein Modulation Drug Pipeline

Nurix Therapeutics, Inc. recently announced it has closed an oversubscribed $120-million financing. The round was led by Foresite Capital with participation from Bain Capital Life Sciences, Boxer Capital (Tavistock Group), EcoR1 Capital, Redmile Group, Wellington Management Company and an undisclosed investor, as well as Nurix's founding investors The Column Group and Third Rock Ventures.

"With the funds raised in this financing, Nurix is well positioned to bring its targeted protein modulation therapeutics into the clinic," said Arthur Sands, MD, PhD, Chief Executive Officer of Nurix Therapeutics. "We will also continue to use our powerful DELigase platform to discover new therapies aimed at previously undruggable targets of high therapeutic potential."

Proceeds from the financing will enable the company to advance Nurix's wholly owned development candidates into clinical development. The leading edge of Nurix's pipeline includes an orally delivered BTK chimeric targeting molecule (CTM) for B cell malignancies for which the company expects to file an IND application with the FDA by the end of the year. The second molecule in Nurix's preclinical pipeline is an orally delivered inhibitor of the CBL-B ligase for stimulation of T cell activation and IL-2 secretion as a novel immuno-oncology agent. Both development candidates were derived from Nurix's DELigase targeted protein modulation platform, which combines the use of DNA-encoded libraries (DEL) with an expanding set of E3 ligases to achieve targeted protein modulation. Nurix's scientific approach enables either the harnessing of E3 ligases to degrade specific target proteins, as in the case of the BTK CTM, or the inhibition of specific ligases to raise substrate protein levels, as in the case of the CBL-B inhibitor.

"Nurix's CTM and DELigase platform technologies have led to the discovery of novel BTK degraders with the potential to transform the treatment landscape for hematological indications," said Michael Rome, PhD, partner at Foresite Capital. "Their differentiated platform and novel approach have resulted in strategic corporate partnerships and we believe position the company as a leader in the emerging protein modulation field."

In addition to advancing its wholly owned pipeline, Nurix recently formed two new strategic collaborations with Sanofi and Gilead to develop novel protein degradation therapies in multiple therapeutic areas. Together, these collaborations provided Nurix with $100 million in upfront payments and the potential for over $4.5 billion in milestones with additional royalties and certain co-development options.

Nurix Therapeutics develops novel therapies that modulate protein levels through small molecule drugs targeting E3 ligases. Nurix's pipeline is focused on developing drugs for immune-mediated diseases and hematologic cancers, including immuno-oncology therapeutics. Nurix was founded by internationally recognized experts in E3 ligase biology and immunology and is funded by leading life science investors and corporate partners.

Zydus & XOMA Announce Exclusive Licensing Agreement

Zydus Cadila and XOMA Corporation recently announced they have entered into a licensing agreement to advance an IL-2-based immuno-oncology (IO) drug candidate that combines Zydus' IL-2 with XOMA's novel anti-IL-2 monoclonal antibody.

As part of the agreement, Zydus will advance the new IO candidate through formal clinical trials. Zydus has been granted exclusive rights to develop and commercialize the therapy in India, Brazil, Mexico and other emerging markets, and XOMA has the potential to receive single-to double-digit royalties on commercial sales in those territories. XOMA retains rights in all other territories (ie, XOMA territory). Through this collaboration, Zydus will develop the new IO drug candidate through human proof-of-concept and each company has the potential to receive pre-defined shares of future proceeds that may arise from licensing and commercialization activities.

Speaking about the development, Managing Director of the Zydus group, Dr. Sharvil Patel said, "IL-2 will be the backbone of IO-based therapies for cancer treatment in the future. In this win-win agreement, we see a great strategic fit between our IL-2 and XOMA's anti-IL-2 monoclonal antibody as together they have the potential to provide a safe and efficacious medicine to address the unmet needs of patients living with cancer."

Jim Neal, Chief Executive Officer at XOMA, added "IL-2 has long been recognized as an effective anti-tumor agent, but its utility has been limited by its toxicity. XOMA has developed unique, fully human antibodies that promote IL-2 action specifically to the cytotoxic effector immune cell populations relevant for anti-tumor activity while simultaneously limiting the unwanted stimulation of immunosuppressive T cells, thereby minimizing its undesired side effects. This IL-2 and monoclonal antibody combination has the potential to turn the immune system against the cancer cells, and Zydus is an ideal partner to advance this combination through clinical development."

Zydus Cadila is an innovative, global pharmaceutical company that discovers, develops, manufactures and markets a broad range of healthcare therapies, including small molecule drugs, biologic therapeutics, and vaccines. Over the last several years, Zydus Biologics has developed significant capabilities in non-clinical, clinical development, scale-up, and manufacturing biologicals, having successfully developed a portfolio of 30+ biologics, with 12 biologics receiving marketing authorization. The group employs nearly 25,000 people worldwide, including 1,400 scientists engaged in R & D, and is dedicated to creating healthier communities globally. www.zyduscadila.com

XOMA has built a significant portfolio of products that are licensed to and being developed by other biotechnology and pharmaceutical companies. The Company's portfolio of partner-funded programs spans multiple stages of the drug development process and across various therapeutic areas. Many of these licenses are the result of XOMA's pioneering efforts in the discovery and development of antibody therapeutics. The Company's royalty-aggregator business model includes acquiring additional licenses to programs with third-party funding

Menlo Therapeutics & Foamix Pharmaceuticals Complete Merger

Menlo Therapeutics Inc. recently announced the completion of its merger with Foamix Pharmaceuticals Ltd. following the satisfaction of all closing conditions required by the merger agreement.

Upon completion of the merger, pursuant to the terms of the merger agreement, Foamix became a wholly owned subsidiary of Menlo. Under the terms of the merger, Foamix shareholders received 0.5924 of a share of Menlo common stock for each Foamix share owned, as well as a non-transferrable contingent stock right. These contingent stock rights potentially allow Foamix shareholders to receive additional shares of Menlo common stock based on the results of Menlo's Phase 3 trials of serlopitant for the treatment of pruritus associated with prurigo nodularis, as more fully described in the companies' joint proxy statement/prospectus on Form S-4. Foamix ordinary shares ceased trading as of the close of trading on March 6, 2020. On March 9, 2020, newly issued Menlo shares will commence trading under the ticker MNLO on Nasdaq.

Since announcing the transaction on November 11, 2019, the company achieved a major milestone with the launch of its first product, AMZEEQ for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in adults and pediatric patients 9 years of age and older. "We are encouraged by the initial performance and activities in support of the launch of AMZEEQ," continued Mr. Domzalski. In the coming weeks, the company anticipates announcing the results of its Phase 3 clinical trials of serlopitant for the treatment of pruritus associated with prurigo nodularis. Additionally, the company expects to announce the results of its Phase 2 clinical trial for FCD105 (minocycline 3% and adapalene 0.3% foam) for the treatment of acne in the second quarter of 2020. The company has also taken meaningful steps towards facilitating a successful integration and capitalizing on expected cost synergies.

Effective upon the closing of the merger, Foamix's management team will manage the Company, led by David Domzalski as Chief Executive Officer.

As part of the transaction, Foamix has designated five of its pre-closing directors, David Domzalski, Sharon Barbari, Rex Bright, Anthony Bruno and Stanley Hirsch to serve as members of the Menlo Board of Directors. Menlo has designated two of its pre-closing directors, Steve Basta, Menlo's Chief Executive Officer prior to the consummation of the merger, and Elisabeth Sandoval, to be directors of the Company following the merger.

Menlo Therapeutics Inc. is a different type of biopharmaceutical company working to solve some of today's most difficult therapeutic challenges in dermatology and beyond.

With expertise in topical medicine innovation as a springboard, the company is working to develop and commercialize a variety of solutions using its proprietary Molecule Stabilizing Technology (MST), and has received FDA approval for the world's first topical minocycline, AMZEEQ. In addition, the company is focused on the development of serlopitant, a once-daily oral NK1 receptor antagonist, as a novel potential treatment option for pruritus associated with prurigo nodularis.

Haselmeier Receives Medical Device Master File Number for Product Platform

Haselmeier officially announced it has received Master File Number MAF3202 from the US FDA for its D-Flex product platform, a new generation of injection pen systems for subcutaneous self-administration.

A device master file provides regulatory authorities with proprietary data about a material, component, or manufacturing process. It enables the company submitting the information to the FDA to comply with regulatory requirements for trading in the US while protecting its intellectual property from potential partners, competitors, and customers. Moreover, it facilitates combination product approvals for multiple applications using the same device.

Haselmeier formally submitted the MAF for D-Flex in late 2019, following productive discussions with the FDA. Pharmaceutical customers can now refer directly to the Master File Number MAF3202 when submitting their own products based on the D-Flex pen for approval, greatly simplifying and streamlining the FDA clearance process.

With this documentation in place, customers worldwide will be able to leverage the patent-registered D-Flex disposable pen system for their combination product development. This versatile, reliable platform is configurable for several fixed doses, bridging the gap between fixed and variable-dose pens, and can support pharmaceutical customers from clinical trials through to commercial use.

Konrad Betzler, Vice President Quality and Alexander Ball, Vice President IT, were involved in the FDA talks. As Mr Betzler comments, "We are delighted that global pharmaceutical customers can now benefit from this device master file submission. The file is a 'living document' that will evolve over the months and years ahead, in line with the latest D-Flex capacity and capability enhancements."

In addition to the D-Flex injection system, Haselmeier also presented its D-Flex Connect system to the FDA. D-Flex Connect comprises the D-Flex pen, a smart cap, and an innovative, future-proof software platform. This development illustrates Haselmeier's active commitment to digitalization. Following positive initial conversations with the FDA, Haselmeier plans to compile the data for either 510(k) or IDE submissions by the end of 2020, with the goal of enabling its customers to deploy D-Flex Connect in clinical trials.

As Mr Ball remarks, "We are grateful to the FDA for their active and encouraging participation in the meetings held so far. This is an important step for Haselmeier's expansion into smart data management for therapy efficiency by building the D-Flex Connect platform."

Haselmeier, headquartered in Switzerland, is a leading provider of subcutaneous injection system solutions. As a reliable development partner, Haselmeier provides customized solutions from concept design and prototyping to engineering and industrialization, including pharmaceutical packaging solutions. Haselmeier empowers safe self-administration of liquid drugs through the development and manufacture of intelligent injection devices that improve therapy efficiency. Moreover, the company is actively developing innovative connected solutions that will help shape the future of smart healthcare.

Todos Medical Enters Coronavirus Nucleic Acid Buccal Testing Kit Distribution Agreement

Todos Medical Ltd. recently announced it has entered into a non-exclusive distribution agreement with 3D Biomedicine Science & Technology Co. for distribution in the US and Israel of 3D BioMed's 3DMed 2019-nCoV Detection Kit (COVID), 3DMed 2019-nCoV & Flu A/B Detection Kit (COVID/Flu) and its proprietary ANDiS350 3DMed Automated Solution countertop real-time PCR machine (3D Machine). 3D BioMed's COVID, COVID/Flu and 3D Machine have received approval from the Chinese FDA and have received a CE Mark in Europe. 3D BioMed is currently engaged in discussions with the FDA regarding approval of its products.

"I am very pleased to help Todos and 3D BioMed bring this technology forward for commercial launch in the US under CLIA, and help support FDA approval for 3D BioMed's suite of products here in the US as quickly as possible," said Jorge Leon, PhD, Chief Medical Advisor to Todos. "The main differentiation in the 3D BioMed offering vs. other nucleic acid PCR-based testing is the influenza A and B tests combined with coronavirus testing. This is a clinically meaningful combination because of the extended flu season in the US that will create additional doubt among healthcare providers regarding the cause of symptoms for patients. The fact that this will be available in one testing paradigm seems to be novel in the US."

Concurrent with this announcement, Todos and Provista Diagnostics, Inc. have agreed to use Provista's lab in Alpharetta, GA, to conduct the CLIA validation required to launch the test in the US.

Rao Mulpuri, PhD, MBA Chief Operating Officer of Provista, commented "Todos Medical and Provista Diagnostics will work together to complete the validation and make the product available to healthcare providers in a timely manner."

3D BioMed has shipped materials to the Provista lab in Georgia in order to support the validation being conducted over the coming weeks.

"PCR is the current gold standard for diagnosing novel coronavirus in the United States and abroad," said Gerald Commissiong, President & CEO of Todos. "We believe 3D BioMed's 3D Machine and kits provide some of the best results in the market because of the engineering applied in establishing the automation that reduces variability and human error in the lab, while significantly increasing throughput. We intend to work expeditiously to validate this technology at Provista, so that we can come online in the US and add additional critically needed testing capacity to the nation's infrastructure. We will be targeting nursing homes, senior care centers, and ensuring that governments have access to our testing capabilities for their constituencies."

Itamar Medical & Clalit Research Institute Establish Research Collaboration

Itamar Medical Ltd. recently announced it has entered into a research collaboration agreement with Clalit Research Institute (CRI), a subsidiary of Clalit Health Services (CHS), Israel's largest state-mandated health service organization.

Under the agreement, Itamar and CRI will collaborate to conduct a study designed to determine if data from the WatchPAT signal can help predict cardiovascular health outcomes. The study will use artificial intelligence tools to compare predictive models for different outcomes, such as cardiovascular disease, atrial fibrillation, congestive heart failure, and other outcomes. Approximately 50,000 patients within the CHS network have undergone WatchPAT testing over the past 10 years. As a state-mandated health services organization, CRI has access to comprehensive patient health medical records and demographic and longitudinal follow-up data going back 20 years for most of these patients with WatchPAT data.

"The association between sleep-disordered breathing and serious health outcomes is well documented, yet data typically collected from overnight sleep studies are summarized into a small number of reported metrics," said Gilad Glick, President and Chief Executive Officer of Itamar Medical. "We believe that the data contained in the WatchPAT raw signal recorded over the entire night has tremendous potential not only to aid in the diagnosis of sleep apnea and help phenotype patients, but also to predict serious cardiovascular health outcomes. As the largest state-mandated health service organization in Israel, CRI has access to a trove of patient data that will, for the first time, allow us to explore the predictive potential of our WatchPAT technology. We look forward to collaborating with CRI to explore how WatchPAT may play a role in improving healthcare outcomes across a wide range of indications."

The study will be conducted in four phases that include data acquisition; extracting appropriate study populations for each healthcare outcome evaluated; baseline modeling using electronic medical record (EMR) data and published literature; and WatchPAT signal modeling using artificial intelligence and machine learning to integrate WatchPAT signal data and EMR data. The study is anticipated to take 2 years.

"Signal processing can capture "hidden" objective features connected to a variety of diseases. We are excited to evaluate its potential to predict a wide array of cardiovascular diseases. If the model will prove itself; it will be a huge potential to expand this model globally to other healthcare systems especially in poor countries with no well-established EMR systems," added Prof. Ran Balicer, the Director of Clalit Research Institute.

Itamar Medical is engaged in research, development, sales and marketing of non-invasive medical devices for the diagnosis of respiratory sleep disorders and uses a digital healthcare platform to facilitate the continuum of care for effective sleep apnea management with a focus on the cardiology market. Clalit Health Services is the largest healthcare organization in Israel, providing primary, specialty, and hospital care to over 50% of the Israeli population, with minimal attrition throughout members life.

TTP Enters Exclusive License Agreement With DiaSorin

TTP plc and DiaSorin have recently signed an exclusive license and technology transfer agreement. DiaSorin will combine its extensive molecular test offering with TTP's Puckdx platform to develop a single-use, sample-to-answer, molecular diagnostics point-of-care platform for human IVD applications.

TTP's proprietary Puckdx platform offers a flexible, fast time-to-result and low-cost solution for translating diagnostic assays for human and animal health and life science research to an easy-to-use desktop device. TTP's Puckdx is based on a unique disposable robotic pipette system with a fast PCR module, combined with a cartridge containing all the necessary reagents.

Using this simple and cost-effective technology solution in combination with DiaSorin's human IVD assays could provide clients with a result in less than 15 minutes. This could help to decentralize testing, which in turn could make diagnostic services more affordable and convenient for patients and reduce the time from diagnosis to treatment to help prevent the spread of infectious diseases.

Giles Sanders, Consultant at TTP, said "We are delighted that DiaSorin has chosen Puckdx as their preferred POC platform. We look forward to working in close partnership with DiaSorin to rapidly commercialise the platform, benefiting patients and healthcare providers worldwide."

Piers Harding, Consultant at TTP, added "During the development of the Puckdx platform, we have focused on a system that enables easy transfer of assays and a reliable and readily manufactured disposable. We are excited to have such a major diagnostic company wishing to bring the platform to market for human applications. The opportunity to utilise Puckdx for other fields of application continues to be available, and we would be keen to collaborate with key players developing assays in areas such as for animal health and low-cost lab robotics".

TTP's Puckdx platform is based on a unique disposable robotic pipette system with a fast PCR module, combined with an easy-to-use cartridge containing all the necessary reagents. For more information, visit https://www.ttp.com/desktop-biology.

TTP is an independent technology company where scientists and engineers collaborate to invent, design, and develop new products and technologies. Working across a wide spectrum of industries including health, telecoms, industrials and consumer, TTP creates breakthrough solutions that bring strong commercial value to clients and the benefits of technology to all.

Headquartered in Italy and listed in the FTSE MIB Index, DiaSorin is a global leader in the In Vitro Diagnostic (IVD) field. For over 50 years the Company has been developing, producing and marketing reagent kits for IVD worldwide. Through constant investments in research and development, and using its own distinctive expertise in the field of immunodiagnostics to deliver a high level of innovation, DiaSorin offers today the broadest range of specialty tests available in the immunodiagnostics market and new tests in the molecular diagnostics markets, which identify DiaSorin Group as the "Diagnostic Specialist."


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2019 Global Drug Delivery & Formulation REPORT

Part Two of a Four-Part Series

Part 1: A Review of 2019 Product Approvals

Part 2: Notable Drug Delivery and Formulation Product Approvals of 2019

Part 3: Notable Drug Delivery and Formulation Transactions and Technologies of 2019

Part 4: The Drug Delivery and Formulation Pipeline

By: Josef Bossart, PhD, Executive Editor, PharmaCircle LLC

Introduction

This is the fourth edition of the report's Notable Drug Delivery and Formulation Product Approvals, and the most challenging from an editorial perspective. In previous years, it was possible to identify 10, 20, or even 30 approvals that reflected a new or existing drug delivery technology in new or clinically important ways. That wasn't the case for 2019. While many products were approved using a variety of drug delivery and formulation technologies, very few qualified as notable. This year, we have decided to limit this section to four approvals.

Perhaps drug delivery has just been in a resting phase in terms of technology and novel product development for the past decade. Technology in general is marked with leaps and rests. When was the last time you really needed the technology benefits offered by a new computer, television, or microwave oven? The auto industry seems to be breaking out of a decades-long technology rest with self-driving and electric vehicles. Auto styles and colors may change annually, but for decades we were offered the same vehicles with a new design and a few more creature comforts. It seems to be the same with drug delivery technologies. What worked in 1985 still works in 2020, perhaps with somewhat better performance, but little else. The most exciting potential drug delivery technology of the past two decades, inhaled macromolecules, has largely failed and been supplanted by patient-friendly autoinjectors. Better, but not really notable in 2019.

The four selected products, using technologies developed as much as decades ago, provide insight into the future of therapeutics and business. Zolgensma, Novartis' gene therapy for the treatment spinal muscular atrophy is perhaps the first significant step in validating gene delivery and expression as a viable therapeutic option for simple genetic diseases. Janssen's Spravato is notable less for the nasal delivery technology than the elegance of its solution to a pressing medical need. Rybelsus, the first non-injectable macromolecule likely to achieve widespread use and commercial success may also close the door behind it, at least with this generation of macromolecule absorption enhancers. What's next? Aurora's High CBD Drops points to a parallel future when the increasing sophistication of botanicals competes directly with more traditional pharmaceutical products.

Is there a technology revolution sitting on a lab bench or in the clinic? That will be subject of the next two parts of this report. Let's appreciate for now what 2019 has delivered.

Spravato (Janssen Pharmaceuticals, Inc.)

Active: Esketamine HCl (274 Daltons, salt)
Molecule Type: Small Molecule
Indication: Treatment Resistant Depression
Delivery Route: Nasal
Dosage Form: Nasal Solution
DD Category: Nasal Spray Pumps/Devices
Dosing: Twice per Week, then Once per Week
First Approval: 2019-03-05 (USA)
Technology: Aptar BiDose Systems
Technology Owner: Aptar Pharma

Development Summary

The first evidence of Spravato clinical development is a Pre-IND meeting held with the FDA May 2012. Janssen-sponsored trials of intravenous esketamine, the s-isomer of the previously approved racemic ketamine, for treatment-resistant depression were initiated June 2012. The first intranasal studies with patients, pharmacokinetic studies, were initiated in the second half of 2013. Dosages for intranasal trials were agreed with the FDA in December 2014. The new drug application was filed September 2018, and approval was received March 2019. Overall development, from the time of first regulatory discussions to approval, was 6.8 years. The clinical and regulatory pre-NDA filing period was 6.3 years. Spravato is classified by the FDA as a new active ingredient rather than a new molecular entity.

Platform/Technology Summary

Aptar's BiDose nasal device is, as the name suggests, indicated for the administration of two doses, generally one dose in each nostril. The device can be used with both liquids and powders and is not primed before use. Maximum liquid volume is 0.1 ml, which is the case with Spravato. Dosing is two doses of 14 mg per nostril (two devices required). A total of six other products using the BiDose technology have been identified as in clinical development. The most advanced BiDose technology-based pipeline product is Milestone Pharmaceuticals' MSP-2017 (etripamil) in Phase 3 development.

Formulation Summary

Spravato is a water-based formulation with 28 equivalent milligrams of base esketamine hydrochloride (32.3 mg) in 0.2 ml. The excipients are citric acid, edetate disodium, sodium hydroxide, and sterile water for injection.

Reflections

From a drug delivery and formulation technology perspective, there is nothing remarkable about Spravato. The BiDose device offers a number of patient benefits but nothing evolutionary, much less revolutionary. The importance of Spravato rests with its ability to provide patients with a more convenient dosing option that can encourage treatment and compliance. The use of intravenous racemic ketamine for the treatment-resistant depression has achieved considerable popularity as an off-label use of the drug. Intravenous administration can vary from 5 minutes to 2 hours in a clinical facility setting. From a cost perspective though, intravenous ketamine may be a cheaper option for many patients given the $650 per dosing (two devices) price for Spravato, not including physician costs, about $32,000 per year. This compares with $400 or so for a single weekly or bi-weekly ketamine infusion session. Spravato forecasts vary widely from $600 million to $3 billion annually at peak.

Spravato may be a small step forward in drug delivery and formulation technology application, but it provides an important benefit for patients and the Johnson & Johnson bottom line.

Rybelsus (Novo Nordisk Inc.)

Active: Semaglutide (4,114 Daltons)
Molecule Type: Peptide Conjugate
Indication: Glycemic Control, Adults Type 2 Diabetes
Delivery Route: Oral
Dosage Form: Oral Tablet

DD Category: Oral Peptide/Protein/ Macromolecule Receptor Carrier
Dosing: Once Per Day
First Approval: 2019-02-20 (USA)
Technology: Eligen Technology
Technology Owner: Emisphere Technologies, Inc.

Development Summary

The first evidence of clinical development is a December 2009 safety and pharmacokinetic trial in healthy subjects. A series of safety, tolerability, and pharmacodynamic trials followed leading to efficacy and dose-ranging studies starting in 2016. The new drug application was filed with the FDA in March 2019 followed by approval September 2019. The time from the start of clinical activity to approval was 9.8 years, with 9.2 years spent in the clinical development stage.

Platform/Technology Summary

The Eligen technology has a long history with multiple product failures and a single marketed product, Eligen B12, approved as a medical food, prior to Rybelsus' approval. First announced in 1994, the Eligen technology has been previously applied without success to calcitonin and heparin. The partnership with Novo Nordisk related to GLP-1 Receptor Agonists goes back to 2008. There appear to be no additional Eligen-based products in active clinical development.

Formulation Summary

Rybelsus is approved as 3-, 7-, and 14-mg tablets with the Eligen absorption-enhancing excipient, SNAC. The approved dosage forms contain magnesium stearate, microcrystalline cellulose, kovidone, and salcaprozate sodium. All dosages use the same 300 mg of salcaprozate sodium. The product has a number of restrictive conditions related to dosing. The prescribing information requires Rybelsus to be taken 30 minutes prior to a meal. The meal is required, it is not an empty stomach requirement. Varying from the recommended dosing results in lower (meal too early) or higher (meal too late) absorption of the active. Bioavailability is stated as 0.4%-1.0%.

Reflections

Rybelsus represents the first true oral macromolecule targeted to a large patient group. The Eligen technology appears to be sufficiently efficient to allow for efficacy with an acceptable safety profile. The real magic here may be the manufacturing efficiencies that permits pricing to be on the order of the injectable despite a 1% bioavailability. Big Pharma is loath to compromise on margins, but with exclusivity in the oral GLP-1 market, a recent approval recommendation in Europe, the prospect of an obesity claim, and forecast annual sales exceeding $3 billion, a compromise on cost of goods is more than acceptable. For the Eligen technology, it seems that Emisphere hit the jackpot on its last nickel.

Zolgensma (AveXis, Inc, Novartis Pharmaceuticals Corp.)

Active: onasemnogene abeparvovec-xioi
Molecule Type: AAV9 Vector Based Gene Therapy
Indication: Spinal Muscular Atrophy (SMA)
Delivery Route: Injection, Intravenous Infusion
Dosage Form: Injection Suspension
Dosing (Duration): Single Infusion (One Hour)
DD Category: Adeno-Associated Virus Vectors, Brain Targeting
First Approval: 2019-05-24 (USA)
Technology: NAV Vectors, AskBio Self-Complementary Vector, Genethon AAV Vector
Technology Owner: Multiple

Development Summary

Clinical-stage development started with a Pre-IND meeting December 2011 followed by an IND submission August 2013. Patient trials were initiated in May 2014 with a gene transfer trial to evaluate safety and efficacy. The BLA was filed November 2018 and received a priority review. The time from first FDA interaction to approval was 7.4 years, including a 6-month review.

Platform/Technology Summary

As is the case with all gene and cell therapy products, Zolgensma depends on multiple technologies from multiple companies. The core underlying technology is based on the NAV Vector technologies, including AAV9, associated with the University of Pennsylvania and the laboratory of Jim Wilson. RegenXbio appears to hold an exclusive license to the NAV Vector platform. Developed in the early 2000s, there has been some recent frustration expressed that the current generation of AAV technologies have seen little advancement since then.

Formulation Summary

Zolgensma is provided as an injection suspension in 5.5-ml and 8.3-ml vials with a nominal concentration of $2.0x10^{13}$ vector genomes per ml. Excipients include Poloxamer 188 (0.005%), magnesium chloride (1 mM), Tris (20 mM), and sodium chloride (200 mM).

Reflections

Zolgensma has elicited significant medical, regulatory, and public attention as a result of its purported clinical benefits and high price, $2.1 million per patient. Despite the high price, there is health economics support for a price in excess of $1 million for this potentially life-transforming treatment. It will be interesting to see if Novartis can recapture the $8.7 billion it invested in purchasing AveXis, the developer of Zolgensma. There are only a limited number of infants born with the condition, about 1 in 10,000, and many fewer individuals, drug plans, and governments able to afford the $2.1-million price tag. The hope it seems is that the AveXis platform technology can be applied to additional indications with larger populations and similar pricing elasticity. Two identified AveXis projects, AVXS-201 for Rett Syndrome and AVXS-301 for ALS, were in preclinical development at the time of the last public announcement (2018). Zolgensma is currently being studied for intrathecal administration.

Aurora High CBD Drops (Aurora Cannabis Inc.)

Active: Cannabidiol (314 Daltons)
Molecule Type: Small Molecule
Indication: Severe Epilepsy
Delivery Route: Oral
Dosage Form: Oral Liquid (60mg/ml)
DD Category: Oil Formulations
Dosing: As Required
First Approval: 2019-12-02 (Ireland)
Technology: Not Described
Technology Owner: Aurora Cannabis

Development Summary

There is no clinical development information available, and there likely was no formal development beyond basic quality and stability studies. The product, a 60% w/v oil formulation of cannabidiol (CBD), was added to the Irish Medical Cannabis Access Programme in 2019. It is reasonable to expect the company was required only to provide composition and purity documentation.

Platform/Technology Summary

The Irish authorities and Aurora Cannabis offer little information in terms of the formulation beyond simple concentration information. Product information at the company's website for a similar product claims "no fillers or dilutive agents." Aurora Cannabis, operating in Canada where cannabis was legalized in 2019, sells CBD and THC in a variety of formulations, including Cannabis Oil, Softgels, Oral Dissolve Strips, Edibles, and Vaporizers.

Reflections

The Aurora High CBD Drops approval in Ireland is a high-profile example of how a number of jurisdictions are handling pseudo-pharmaceutical products. Aurora's product, without the clinical development and regulatory burden associated with formal drug approvals seems set to compete directly with GW Pharmaceuticals' Epidiolex, which was approved September 2019 in Europe. The Irish clinical guidance documents for the Cannabis for its Medical Use Access Programme explicitly note use for Dravet and Lennox-Gastaut syndrome, the Epidiolex- approved indications. From a pricing perspective, the Canadian consumer price for the Aurora product of about CDN $100/gram (~US $80), offers a 30% discount to the published US Epidiolex price of US $120/gram. The Irish pricing is not available.

Going well beyond the typical botanical type of preparation where plant material is dried, ground up, and offered as powders or stuffed into capsules, these pseudo-pharmaceuticals often go through significant processing, purification, and standardization before being compunded into a variety of dosage forms using drug delivery and formulation technologies. From an industry perspective, this may well be an indicator of future trends. With a sheen of validated efficacy, availability without a prescription or even a physician visit, and the aura of "natural," these standardized plant-based "therapeutics" will be irresistible to many consumers without drug plans, those who are suspicious of multinational pharmaceutical companies, and others who want to try a different approach to their condition.

The opportunity of pseudo-pharmaceuticals is validated by the number of these products with combined estimated annual sales of $40 billion. Cannabis companies are jumping on the opportunity of wider use of CBD and THC products by licensing and filing patents on a variety of delivery technologies to create their own proprietary dosage forms. And cannabis is not the only opportunity. A search for St. John's wort preparations online finds numerous dosage forms available, including capsules, tinctures, liquid capsules, topical oils, gummies, extracts, and teas, some of which are available as concentrated and extended-release presentations. There are even Kosher versions.

The Irish approval may well be validation of a global move toward non-prescription botanicals as first choice therapeutics. For consumers and governments, the price is right. For companies, the opportunity is attractive with very limited regulatory demands and a quick path to market. Do high-priced niche products like Spravato and Zolgensma define the future of the innovative pharmaceutical industry where good enough is good enough if the price is right? It seems the same old, same old, will no longer suffice to deliver enhanced patient benefits and sustained industry profitability.

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Formulation Forum

Rational Design & Development of Lipid-Filled Hard Capsules

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

Jim Huang, PhD
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With ever increasing percentage of water-insoluble (BCS II/IV) or low permeable (BCS III/IV) new therapeutic entities among drug pipelines, lipid-based drug delivery systems, together with two other main drug delivery technologies, ie, nano and amorphous systems, have become an important tool for the formulation development of those compounds. Lipid-based drug delivery systems enhance the oral bioavailability of drugs via three main mechanisms: (1) increasing dissolution and solubility by pre-dissolving drugs in lipid carriers, (2) increasing drug permeability in the GI tract by inhibition of P-gp and other efflux transporters, and (3) bypassing the first-pass metabolism of the drug through the lymphatic absorption processes. In addition, lipid-based drug delivery systems have the potential to decrease the food-effect and to increase reproducibility of the pharmacokinetic profile of those orally administered drugs by reducing erratic absorption.

A lipid-based drug delivery system typically is composed of a lipid carrier, cosolvent, surfactants, and co-surfactant. Depending on the surfactant level, it can be classified into (1) microemulsion (thermodynamic stable lipid concentrate with high level of surfactant); and (2) nano-emulsion, which is a pre-formed nano-system as a result of high-energy inputs and is kinetic stable in the aqueous phase.

Lipid-based drug delivery systems can be also characterized into the following five categories (Table 1). The two most popular systems used for insoluble drugs are Type II/IIIA: Self-Emulsifying Drug Delivery Systems (SEDDS) and Type IIIB: Self-Microemulsifying Drug Delivery Systems (SMEDDS), forming microemulsions that are thermodynamically stable.

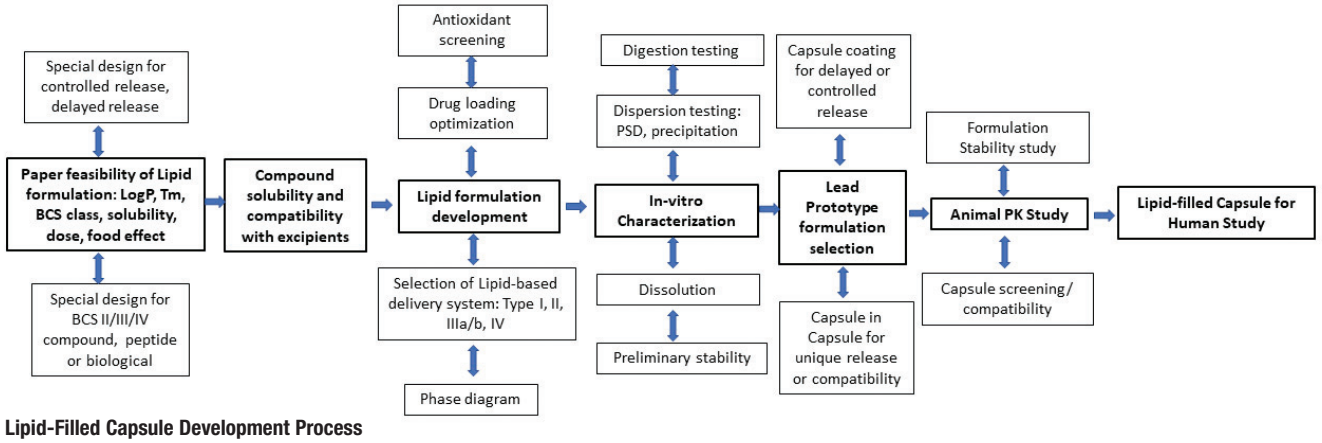
TABLE 1

	Type I: Oil Solution/Suspension	Type II: SEDDS	Type III A: SEDDS or SMEDDS	Type III B: SMEDDS	Type IV: W/O Oil Micelles
% Oil Level	100	40-80	40-80	<20	
% Water Insoluble Surfactant (HLB<12)	-	20-60			0-20
% Water Soluble Surfactant (HLB>12)	-	-	20-40	20-50	30-80
Co-Solvent	-	-	0-40	20-50	0-50
Significance of Aqueous Dispersion	Limited or No dispersion	Rapid dispersion, no loss of solvent capability	Rapid dispersion, some loss of solvent capability	Rapid dispersion, some loss of solvent capability	Rapid dispersion, significant loss of solvent capability
Requirements of Enzymatic Digestion	Required	Maybe	May not necessary	May not necessary	Not required
Droplet size after dispersion	Coarse	100-250 nm	100-250 nm	50-100 nm	<50 nm

*** adaption from Pouton, C.W et al., Eur. J. Pharm. Sci. 2000, 2006, Adv Drug Deliv Rev., 60: 673-91, 2008**

Classification of Lipid-based Drug Delivery System*

FIGURE 1



Lipid-Filled Capsule Development Process

RATIONAL DESIGN & TECHNICAL FEASIBILITY

In order to ensure successful formulation development of lipid-based dosage forms, a thorough understanding of compound properties and a well-defined quality-by-design and development process (Figure 1) should be implemented.

Target Pharmaceutical Profiles

Compounds that will benefit most from lipid-based dosage forms are lipophilic, insoluble drugs that are poorly bioavailable through GI absorption (BCS II) and has a strong food effect. In some cases, the oral bioavailability of therapeutic entities, which are subject to efflux, high first-pass, low stability in GI fluids, or low permeability, such as peptides, biologicals, or BCS III/IV compounds, can be also improved by using lipid-based formulations. For drugs targeted to the intestine/colon, delayed release due to gastric irritation, or sustained release to achieve prolonged PK profile, utilizing solid/semisolid lipid materials or coating of capsules with insoluble or enteric polymer may be employed to achieve those goals. Typically, the ratio of therapeutic dose (mg) to the solubility (mg/mL) in the lipid carrier should be less than 0.5-5 mL to avoid pill burden; compounds with a low-medium dose requirement, log P>2, and a mid-low melting point will have a higher chance of success using the lipid formulation approach.

Solubility & Compatibility of Drug-Excipients

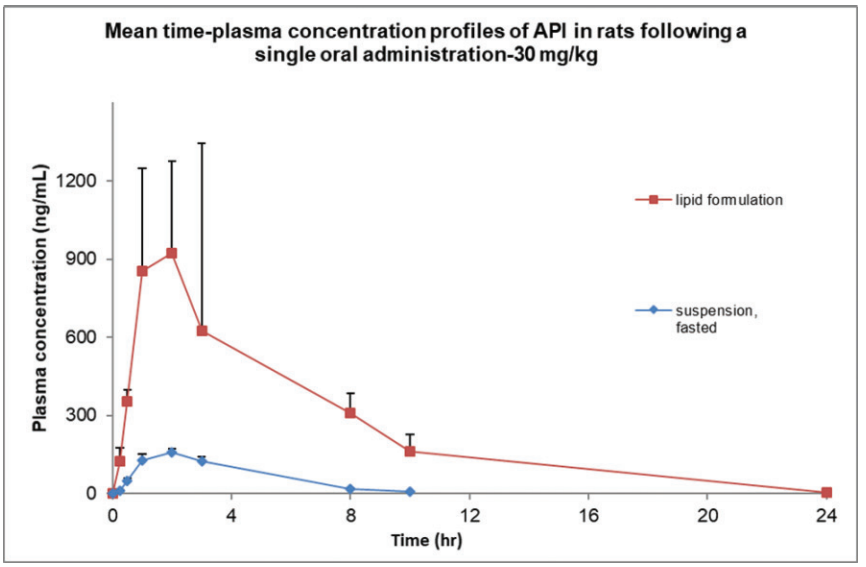
These lipidic excipients can be divided into the following categories: 1) oils such as long-chain triglycerides (LCTs), medium chain triglycerides (MCTs), mixture of mono-, di-, and tri-glycerides, and fatty acids; 2) water-insoluble surfactants: HLB < 12; 3) water-soluble surfactants: HLB ≥ 12; and 4) cosolvents. About 5 to 6 each of oils, surfactants, co-surfactant, and co-solvent (such as corn oil, soy bean oil, sesame oil, olive oil, castor oil, miglyol 812, captex 500 , Solutol, labrasol, cremophor EL, poloxamer 188, Tween 20, Gelucire 44-14, TPGS, Tween 80; Phosal, Span 80, Span 20; Imwitor 988, Capryol 90, Lauroglycol 90, plurol oleic CC497, Labrafil M1944CS, Glycerin, Transcutol , PEG400, ethanol, propylene glycol) and their combinations can be selected and screened by drug solubility and compatibility. For compounds with poor permeability or efflux potential, the excipients that potentially can inhibit enzymatic efflux, increase tight junction permeability, or enhance lymphatic absorption can be added into the solubility screening study. Antioxidant(s) may be also introduced to protect the active drug from degradation due to incompatibility between drug and excipients.

Lipid Formulation Development & Characterization

The success of lipid-based formulations depends on the understanding of the compound's physical-chemical and biopharmaceutical properties. For insoluble compounds with solubility- or dissolution-limited absorption processes, Type II-IV formulations could significantly improve its bioavailability by reducing the droplet size to the nano levels. For example, cyclosporine A lipid dosage form, Neoral®, is a Type III formulation that has a higher bioavailability than its Type II formulation (Sandimmune®). However, smaller droplet size does not always guarantee better in vivo performance. For example, Type I formulation of a lipophilic compound may promote lymphatic absorption and perform best in vivo, whereas a SMEDDS formulation may fail to improve its bioavailability due to precipitation of compound in the GI tract.

Based on an initial excipients screening study, a combination of excipients, solvents, and solubilizers can be used to enhance drug loading. Miscibility of excipients should be assessed using a physical stability study. In some cases, a DOE design can be utilized to screen antioxidant(s) and stabilizer(s) if the

FIGURE 2



Enhancement of Compound Bioavailability (>10 folds) by Lipid-Based Formulation

compound's degradation in formulations is significant. The construction of phase diagrams is very valuable for optimizing self-emulsifying lipidic formulations (Type II-III A/B), defining the boundary of region where microemulsions forms.

Type I formulations consisting of single oil or oil mixtures require enzymatic digestion to be dispersed into oil droplet or micelles. Type II-III can be dispersed by itself in the aqueous medium into emulsion of different sizes with or without the help from enzymes due to utilization of surfactants. Type IV utilizes surfactants, and cosolvents without lipid oils can form micelles of <50 nm. However, due to potential risk of compound precipitation in the GI tract for Type II-IV formulations, an in vitro dispersion and in vitro dissolution in simulated GI fluids (FaSGF, FeSGF, FaSSIF, FeSSIF) should be employed during formulation screening and prior to animal studies.

Dosage Form Development

Based on the stability study and animal PK results, a lead prototype formulation can be selected for further development. To provide a dosage form that is commercially viable and convenient for human consumption, the lipid-based formulation can be filled into capsules and further packed into bottles or blisters. Due to manufacturing complexity and potential leaching of active compound into the shell, softgel capsules are normally not the first choice for encapsulation of lipid dosage forms at the early stage of clinical development. On the other hand, hard capsules, which offer flexibility for use from the early to commercial stages of development and different options for trade dress, are frequently chosen for lipid-based formulations. Studies should be conducted to select the type of capsule that is compatible with the formulation, can withstand the filling/banding process, and is stable throughout the shelf-life without causing leakage and brittleness of the capsule shells. In addition, the selected capsules should also be physically strong enough during the coating process, in case it will be coated with enteric polymers or sustained-release polymers to achieve delayed release into the lower GI tract.

A Case Example

A compound was classified between BCS II (low solubility and high permeability) or BCS IV (low solubility and low permeability), which has a log P of ~3 and a meting point of ~120°C. Its aqueous solubility is extremely low, <1 µm/mL. The compound crystalline suspension had very low bioavailability in animal models that did not generate a dose-proportional exposure in the tox study. It was desirable to obtain a tox and human formulation that has an enhanced bioavailability. Based on the assessment of the compound properties, Ascendia's Emulsol® Technology was utilized for lipidic formulation screening and in vitro assessment. Three lipid-based prototype formulations were developed and tested in animal models, resulting in a >10-fold increase in bioavailability (Figure 2). A hard gelatin capsule type that was compatible with the lead formulation throughout the filling, banding, drying, vacuum testing, and storage period was selected and used for cGMP manufacturing of clinical trial materials.

SUMMARY

Due to the benefits of lipid-based drug delivery in enhancing solubility/bioavailability and dosage manufacturing flexibility, lipid-filled capsules have gained popularity for use in clinical studies. Moreover, additional advantages in enhancing permeability, reducing food effects, and protecting therapeutic entities from degradation make the lipid-based dosage form attractive for delivery of small molecule compounds, peptides, RND/DNA, etc. Formulation development companies that specialize in poorly soluble molecules using GRAS material platforms, like Ascendia, can provide a decisive advantage in product formulation without increasing regulatory approval risk. ◆

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THERAPEUTIC PEPTIDES

Continuous Manufacturing of Peptides Could Speed Up Development, Reduce Costs & Improve Quality

By: Jens Bukrinski, PhD, MSc

INTRODUCTION

Despite the many obvious clinical advantages – safety and selectivity, leading to superior safety and efficacy - and the increasing number of commercial successes, the full potential of peptide therapeutics has yet to be unleashed. Estimated to exceed $46 billion by the end of 2025, the global therapeutics market has attracted the attention of key players, such as Eli Lilly, Novo Nordisk, Pfizer, Takeda, and Amgen. One of the barriers to both development and production has been the high cost of the current state of the art batch manufacturing processes. A new manufacturing process lowering the cost and speeding up their development whilst allowing for superior quality could give the development of therapeutic peptides even more momentum.

The following discusses this revolutionary new technology - the µLOT® technology platform - enabling true continuous peptide synthesis. µLOT has already achieved proof-of-principle in synthesis of complex and challenging peptides.

WHAT ARE THERAPEUTIC PEPTIDES?

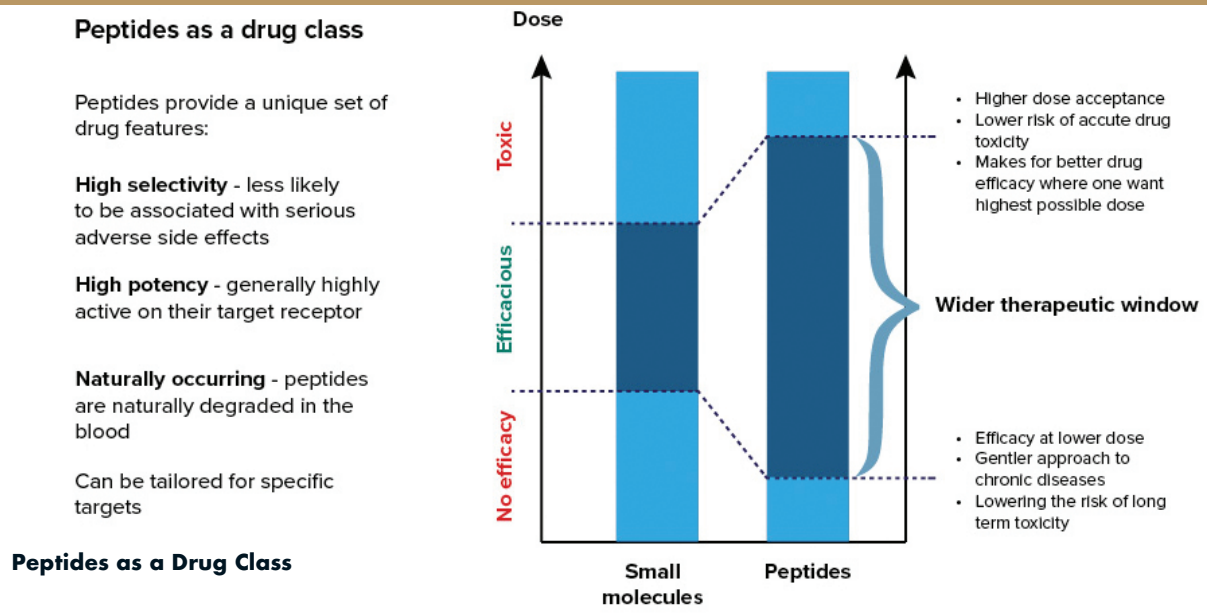
Therapeutic peptides have a long history. Representing a unique class of compounds positioned between small molecules and proteins. The FDA defines a peptide therapeutic as a chain of 40 or less amino acids (the building blocks of both peptides and proteins) and regulates them as small molecules. Therapeutic peptides are designed by rational methods with high specificity to bind and modulate a protein interaction of interest.

Because of the modular design of peptides, which are naturally built from linking together amino acid residues, through peptide bonds, in an end to end fashion, each amino acid is carrying a unique functionality adding a specific property to the peptide. The different amino acid residues are like Lego blocks and enable the design of highly specific drugs.

As a result of their ability to mimic natural pathways, several peptide treatments are essentially "replacement therapies" that add back or supplement peptide hormones in cases where endogenous levels are inadequate or absent. This was evidenced in the 1920s through the isolation and therapeutic use of insulin in people with diabetes.

Despite revolutionizing diabetes treatment, and their known benefits, the appetite for the development of therapeutic peptides was tempered by challenges such as short plasma half-life (most peptides have a half-life of around 15 mins, making these peptides unfit as drugs). As such, they took a back seat to monoclonal antibodies in modern drug development in the beginning of the millennium when the industry learned to produce antibodies in mammalian cells. Most of the low-hanging fruits in antibody therapies have now been developed, and the pharma industry is now looking for the next modality to take its place. The tide is therefore now turning, and the industry has renewed its interest in the development of therapeutic peptides recognizing the benefit they can bring to the treatment of a wide range of conditions. Diversifying from its original focus, the genomic era has allowed for the identification and molecular characterization for many endogenous peptide hormones and their receptors, as such, novel peptidic antagonist and agonist for these receptors are being pursued. Furthermore, novel drug delivery approaches (using non-natural amino acids and or conjugation partners) promotes

FIGURE 1



sustained release and prolonged action, enabling once- daily and once-weekly administration and most recently, technologies enabling oral delivery of large peptides, is seen in late-stage clinical trials.

THE PEPTIDE COMEBACK

Now viewed as a promising and a novel approach to treat many diseases, this renewed interest has led to a number of highly successful "blockbuster" peptide drugs (eg, Copaxone, Victoza or Lupron). As of 2018, more than 100 approved peptide therapeutics for various clinical indications were commercially available in the global market. Additionally, a robust clinical pipeline currently has more than 100 type of therapeutics in late-stage clinical development with more than 200 types of therapeutics in preclinical stage.[1]

Therapeutic peptides have several important advantages over proteins or antibodies: they are small in size and have the ability to penetrate the cell membranes. They also have high activity, specificity, and affinity; minimal drug-drug interaction; and biological and chemical diversity. An added benefit of using peptides as a treatment is they do not accumulate in specific organs (eg, kidney or liver), which can help to minimize their toxic side effects, a considerable benefit to patients.

In the case of cancer, these peptides can be used in a variety of ways, including carrying cytotoxic drugs, vaccines, hormones, and radionuclides.

Valued at $35.2 billion in 2017, the global peptide market is outpacing the growth of the global drug market by two to three times. Increasing demand for efficient and rapid-acting therapeutics for the treatment of cancer and other lifestyle-associated conditions is motivating market growth.

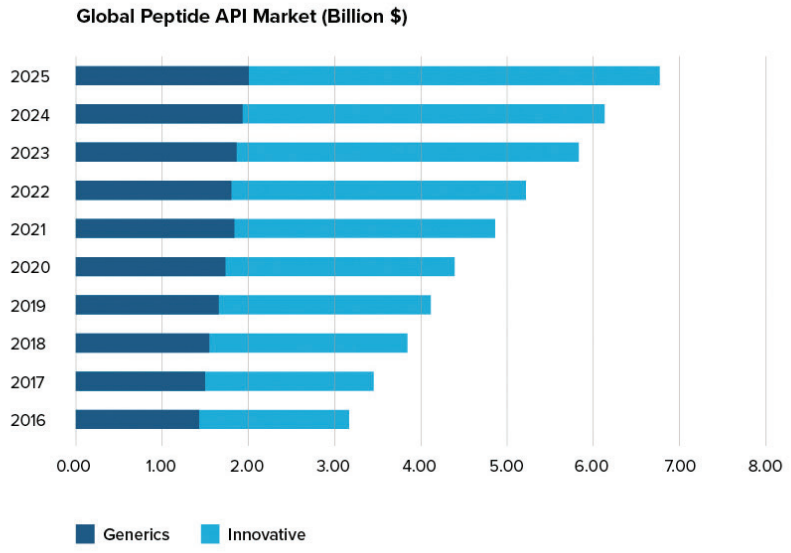
CHALLENGES OF WORKING WITH PEPTIDES

However, it is not all good news as the benefits of therapeutic peptides do not come without their challenges. Currently, peptides require complex synthetic processes in their manufacture, including plant and labor-intensive production cycles. Scale-up of batch processes from preclinical to development and then to commercial is very expensive and associated with significant risk of failure to supply - Failure of a Phase 1 or 2 batch is typically $2.2 million to $5.5 million, depending on dose and number of subjects plus a delay of approximately 1 year.

In addition, batch production processes lack continuous quality and control, increasing batch-to-batch variability, and the risk of the whole batch being discarded is quite high and very costly. The significant steps required to scale up production has led to significant delays in new drugs reaching the market. Many new developments are halted because of the high costs and poor commercial viability that has been associated with their development.

Continuous processing holds the promise of solving a number of critical drawbacks of the current batch manufacturing of therapeutic peptides. By significantly reducing cycle times and labor costs while providing for higher purity and process quality, this technological advance

FIGURE 2



Global Peptide API Market ($Billions)

will drive market growth and spur innovation. The adoption of novel technologies to manufacture efficient drug molecules quickly and with less capital investment is seen as somewhat of a holy grail in this space.

Over and above, this the technology could also significantly reduce the cost and environmental impact of harmful waste as well as energy consumption. The current state-of-the-art in peptide synthesis involves primarily legacy technologies, which use large amounts of highly hazardous reagents and solvents - little focus on green chemistry and engineering. This has attracted growing criticism and pressure to find a cleaner approach.

Currently SB3000's new continuous process has seen a reduction of ~90% in solvent consumption and a similar reduction in the generation of highly toxic waste.

In addition to the environmental benefits, the reduction of toxic waste generation also has significant cost benefits. The current cost of toxic waste disposal in the peptide manufacturing industry is estimated at $1 billion to $1.5 billion based on the annual sales of therapeutic peptides ($20 billion+). By 2025, the cost of the toxic waste disposal will have risen to ~$2.5 billion to $3.5 billion.[2] This does not even take into account that many of the solvents are "listed," meaning that their use is regulated and therefore must be significantly reduced or replaced. The µLOT process would significantly reduce this by about 90%.

A NEW APPROACH TO PEPTIDE MANUFACTURING

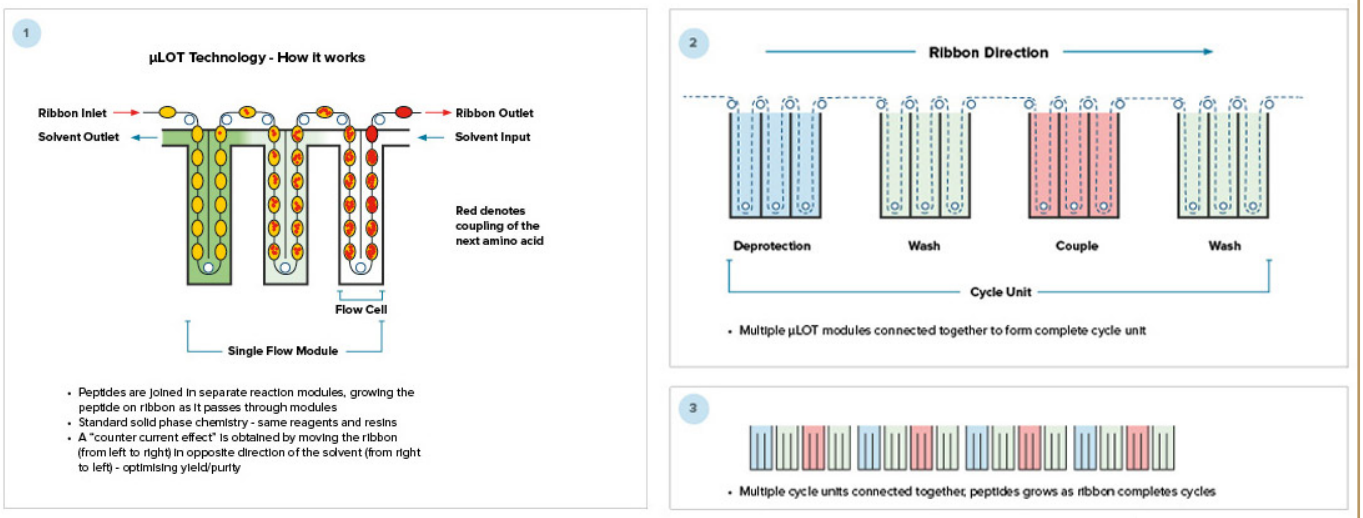
µLOT is an entirely new approach to the manufacturing of therapeutic peptides, which promises to completely replace traditional large-scale batch manufacturing. The µLOT technology platform provides true continuous manufacturing of peptides, enabling in-line process analytical technologies (PAT) throughout the process, providing an unprecedented level of quality and control and a significant reduction in cost of goods. It is estimated that the upstream issues associated with peptide production represents about 75% of the total production costs

The µLOT technology platform is a "chemical assembly line" that uses a ribbon made of polymer mesh that has sachet pockets containing a solid-phase resin and moves continuously through all the various chemical stages of manufacture – all manufacturing stages are on-going at the same time. The ribbon is tailored according to the solid-phase resin, sachet size, and the spacing of the sachets to optimize the process. As the ribbon goes through the manufacturing process, there is very close monitoring of every sachet so that high quality can be ensured through every single step in a continuous fashion. This method enables the same equipment to be used from preclinical through to the commercial phase. As a result, there is no delay and no risk associated with manufacturing development during clinical development.

The µLOT technology platform is a predictable and reliable solution that enables the synthesis of peptides that are not currently economical or technically possible to produce. It will also improve the cost and quality of both novel and current blockbuster peptides due to its in-line process analytical technology. It intends to focus on three commercial segments it believes it can offer the most benefits. These include the following:

- Pharma Companies With Approved Peptides on the Market - By targeting a significant reduction in production costs, improving product quality and enhanced process control, µLOT may enable the drug owner to drive profitability in the remaining in-patent period, while creating a significant competitive advantage during post-patent phase.

FIGURE 3



µLOT Technology – How it Works

- Pharma Companies With Peptides in Early Development - By enabling a seamless progression from small-scale to large-scale production, reducing cost and time to market. Utilizing the µLOT technology in development is anticipated to provide the sponsor with improved product purity profile. The barrier and cost for entry of generic competition can be raised for key development projects, building protective and sustainable measures within core business areas.

- Pharma Companies With Hard-to-Manufacture Peptides - By enabling synthesis of hard-to synthesize peptides at acceptable cost, the µLOT platform could pave the way for more innovative peptide drug designs that currently is not commercially viable.

SUMMARY

The high-quality, high-process consistency between manufacturing runs and the in-line PAT analytics of the µLOT platform will enable unprecedented robustness of the manufacturing process, significantly retiring the risk of failure to supply due to non-scalability of the manufacturing process. Furthermore, in case of process mishaps, the ribbon tracking system will allow the µLOT users to identify exactly what part of the ribbon is out of specification and discard this and in this way, rescuing the rest of the production. In contrast to this, a mishap in a batch process will lead to failure of the entire batch. SB3000 has already seen significant interest in its model, and it is anticipated that the first go-to-market contract will be secured in the very near future. ◆

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BIOGRAPHY

Dr. Jens Bukrinski is Head of R&D at SB3000 and has 20+ years of experience in pharmaceutical development from academia, Novo Nordisk, and Novozymes Biopharma R&D, and as an independent advisor. Having been involved in more than 25 drug development projects and with 5 drugs currently on the market, he has substantial experience in drug development spanning from early stage R&D through clinical development, BLA, and MAA submission and lifecycle management. He earned his MSc in Dairy Science and Technology and his PhD in Structural Biology. After 8 years in academia as post-doc at University of Copenhagen and research associate professor at Carlsberg laboratory studying structure and function of proteins, he moved into the drug development industry. In 2016, he founded CMC assist, providing independent counseling to pharma, biotech, and related industries within CMC development, including regulatory strategy and documentation.

CANNABINOID THERAPY

NeuroDirect Effects™ CBD: Non-Systemic Cannabidiol for Autism Spectrum Disorder

By: Ronald Aung-Din, MD

INTRODUCTION

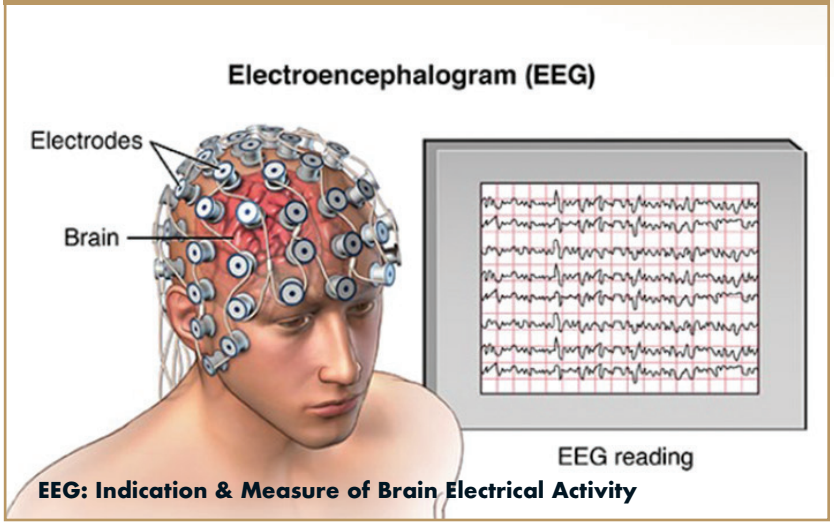
Autism spectrum disorder (ASD) is a disorder of brain development that impacts neural processing in affected individuals. Problems with communication and socialization present challenges for families coping with more severe forms of the disorder. The term "spectrum" in ASD refers to the wide range of symptoms and severity encountered, from gainfully employed "high-functioning" individuals to those severely impaired, requiring continuous care and supervision.[1,2]

ASD generally begins in early childhood, with symptoms eventually causing problems at home and in school. Symptoms of autism often appear within the first year. But some children seem to develop normally then regress between 18 and 24 months of age, when they may suddenly become withdrawn, aggressive, and lose previously acquired language skills and other developmental milestones.

In addition to communication and social interaction problems, ASD patients may exhibit repetitive patterns of behavior. These include but are not limited to the following:

- Speaking with abnormal tone or rhythm
- Repetition of words or phrases verbatim
- Repetitive movements, such as rocking, spinning, or hand flapping, and activities causing self-harm, such as biting or head-banging
- Adherence to specific routines or rituals with difficulties to slightest change
- Problems with coordination and odd movement patterns, such as toe walking, and odd exaggerated body postures
- Unusual sensitivity to light, sound, or touch, yet indifferent to pain or temperature
- Fixating on objects or activities with extreme intensity and focus
- Specific food preferences, refusing those with a certain textures

FIGURE 1



EEG: Indication & Measure of Brain Electrical Activity

In addition to sensory processing issues and sensitivities, accompanying medical conditions that may influence clinical manifestations of autism are seizures, attentional problems, sleep disturbances, gastrointestinal (GI) issues,

and mood disorders, such as impulsivity, agitation, anxiety, and depression.[1,2]

ALTERED BRAIN FUNCTION AS BASIS FOR AUTISM SYMPTOMS: ROLE OF EEG (ELECTROENCEPHALOGRAM)

Signs and symptoms of autism suggest problems in brain sensory processing and outflow from neurochemical and electrical dysfunction. Such abnormalities may be reflected in EEG, electroencephalogram, an objective indication of brain electrical activity, measured through electrodes placed on the skull (Figure 1). The procedure is non-invasive and not painful.

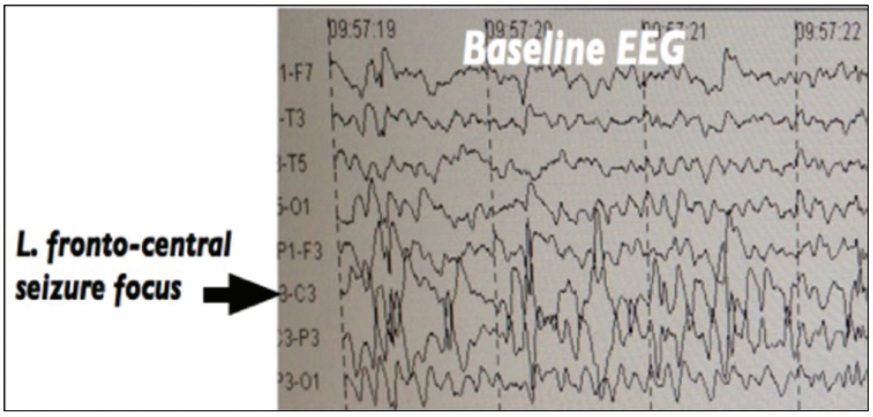
A normal EEG does not necessarily indicate the absence of a brain electrical problem as events, such as seizures and other abnormal electrical activity, may be episodic, occurring intermittently. In ASD, such episodic phenomena may be in the form of seizures of various forms, sudden mood swings accompanied by agitation and impulsivity, staring spells with loss of focus and attention, and repetitive movements, such as grimacing, twitches, flapping, and automatisms involving the lips, face, and hands.

Abnormal brain electrical activity can create specific symptoms, such as stereotyped seizures, staring and inattention, mood swings, agitation, impulsivity, and strange sensations/perceptions, auras, hallucinations, deja vu phenomena, and out-of-body sensations (Figures 2 & 3).[3]

CANNABIDIOL (CBD) AS NEURO-MODULATING AGENT IN AUTISM

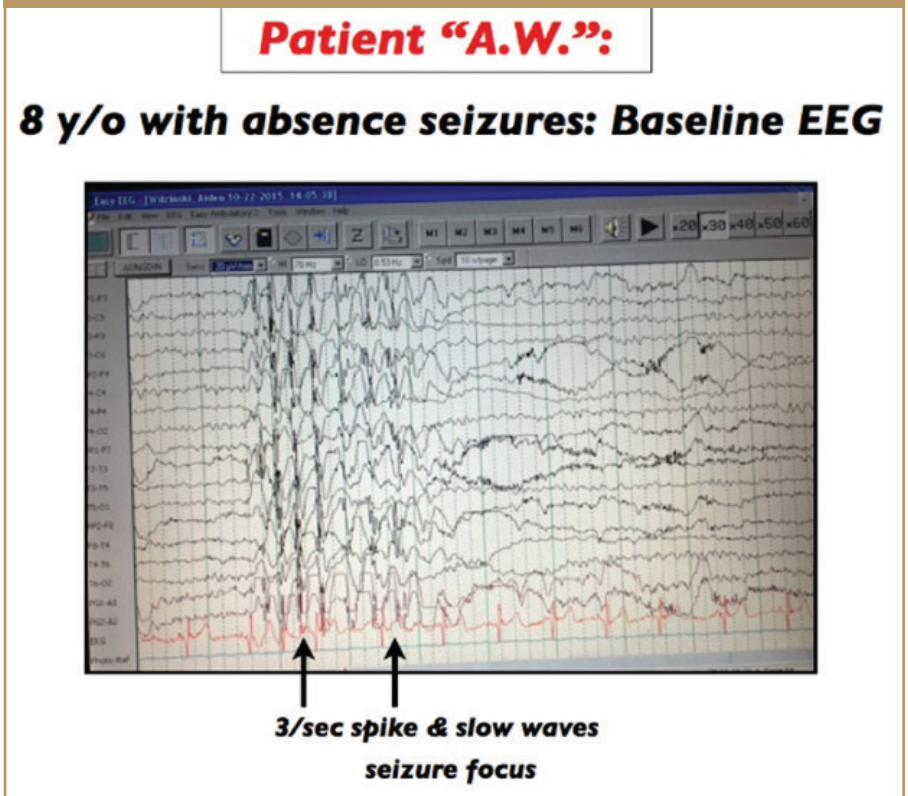
CBD and other cannabinoids have recently become important therapeutic considerations in a number of neuropsychiatric disorders. Starting first with seizures, they are now being used in ADHD, mood disorders, insomnia, Parkinson's disease, and other conditions. Autism spectrum disorder is no exception. Cannabinoids have a wide scope of medical applications as they influence neurotransmission, immune function, and inflammation, and preserve cellular homeostasis and function, among other things.

FIGURE 2



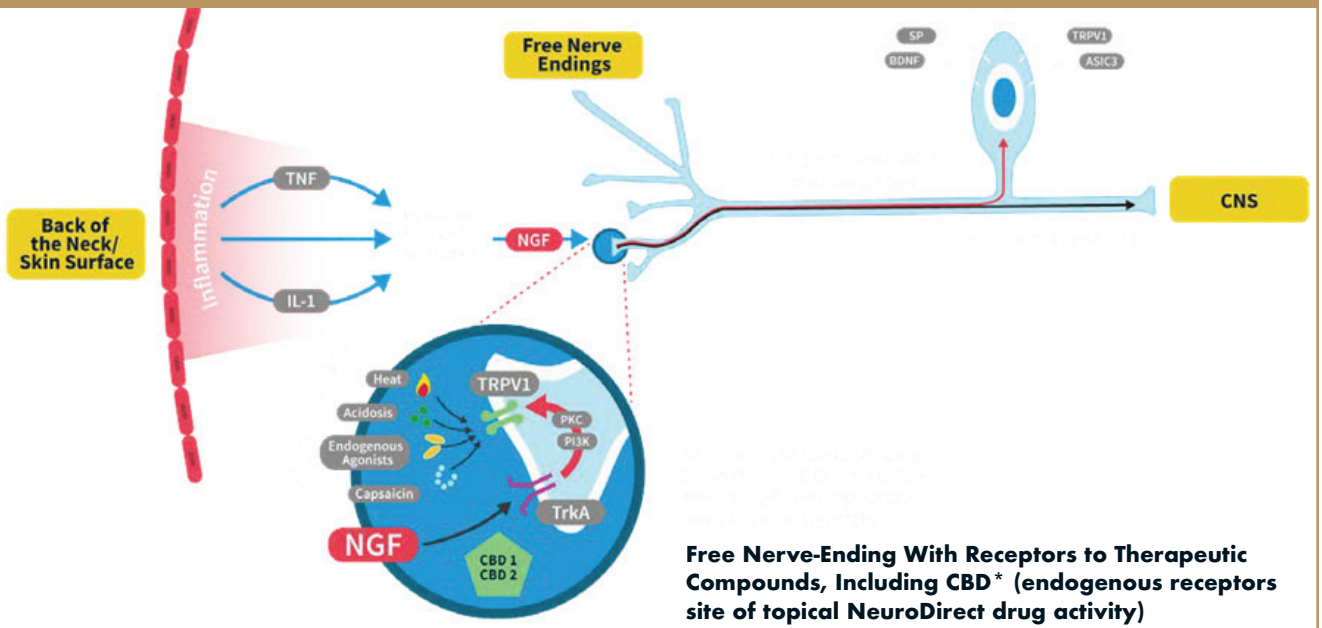
Focal Seizures From Stroke (left brain stroke causing right upper extremity focal motor and sensory seizures)

FIGURE 3



Classic Petit Mal/Absence Seizures (stereotype 3/sec. spike and slow wave absence/petit mal seizures with staring episodes and loss of contact)

FIGURE 4



Free Nerve-Ending With Receptors to Therapeutic Compounds, Including CBD* (endogenous receptors site of topical NeuroDirect drug activity)

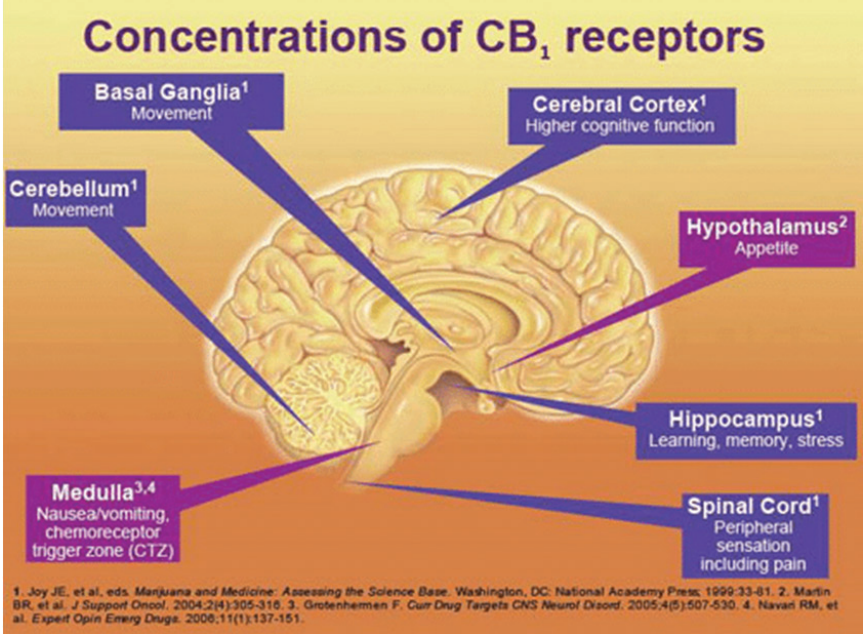
CBD is not psychoactive and does not produce a "high" associated with the cannabinoid THC. CBD's other functions and potential uses include the following:

- Preventing memory loss, which can be associated with THC
- Antipsychotic effects of CBD represent potential treatment of schizophrenia
- Antidepressant and neuro-protective effects
- Decreases symptoms of social anxiety and isolation (useful for autism, fibromyalgia, and PTSD)
- CBD relieves pain by acting on opioid receptors
- CBD treats seizures, inflammation, and nausea

The mechanism of action by which CBD and other cannabinoids exert therapeutic benefit is through activity on CB1 and CB2 receptors of the human endocannabinoid system, ECS. ECS exists to modulate many systems within the body; of particular relevance to ASD are the neurological, immune, and gastrointestinal (GI) systems.

A concern arising from use of cannabinoids in children is potential long-term effects of chronic systemic exposure on developing brains. Non-systemic delivery of neuro-active compounds, including CBD and other cannabinoids, through topical NeuroDirect Effects™ may provide a solution to this potential problem.[4]

FIGURE 5



Cannabinoid Receptors in Various Areas of the Brain

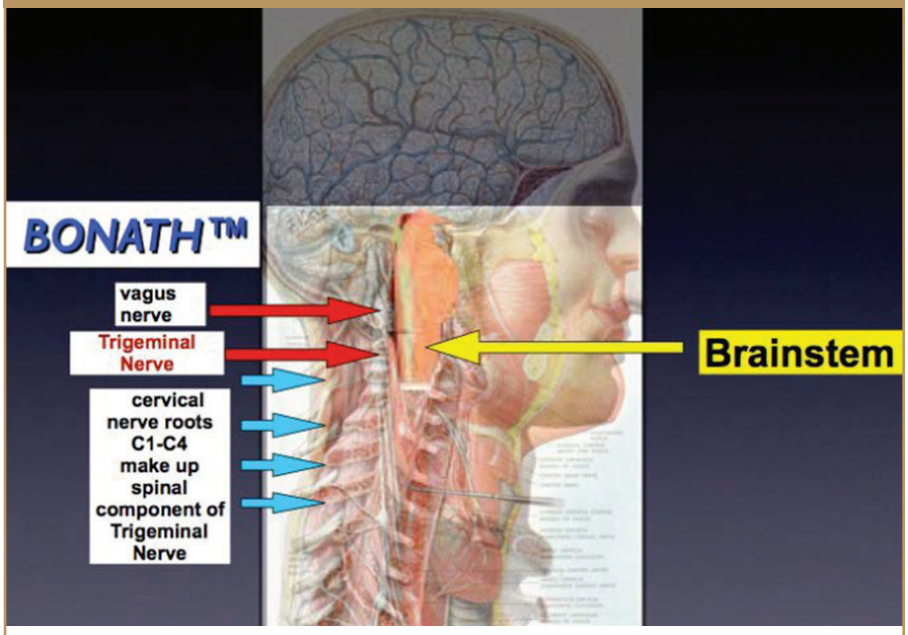
NEURODIRECT EFFECTS TECHNOLOGY™

NeuroDirect Effects Technology is a ground-breaking drug therapy of topically applying neuro-active drugs with therapeutic benefit achieved through action on skin-free nerve-ending receptors with direct communication to the central nervous system (CNS).

As embryonic tissue, neuroectoderm, forms both the CNS (brain and spinal cord) and skin, there exist neuro-chemical receptors on free nerve-endings in skin in communication with the CNS, providing continuous neural information for processing and interpretation. The free nerve-ending is a peripheral end component of spinal cord dorsal ganglia, primary processing site of neural input before entering the CNS. Exposed receptors on cutaneous nerve-endings can be activated by therapeutic compounds applied topically to skin surface. These include receptors to endogenous agonists serotonin, norepinephrine, dopamine, acetylcholine; as well as to endorphins, TRPV1, nerve growth factor; and, CB1 and CB2 receptors to cannabinoids (Figures 4 & 5).

Neuro-active drugs, such as CBD, may be compounded in epidermal penetrating medium to activate cannabinoid receptors on skin nerve-endings, resulting in local neurochemical reaction and formation of nerve action potential to the CNS. Therapeutic effects are achieved as respective brain receptors are activated. Over 40 such compounds have been studied and utilized in this manner, resulting in granting of 10 patents in the US and abroad. Of interest is that in all preparations, therapeutic benefit was realized within 5 to 8 minutes of topical drug application without usual systemic side effects. This is not surprising

FIGURE 6



Relationship of Upper Cervical Nerves at BONATH to Trigeminal & Vagus Nerves & Brainstem

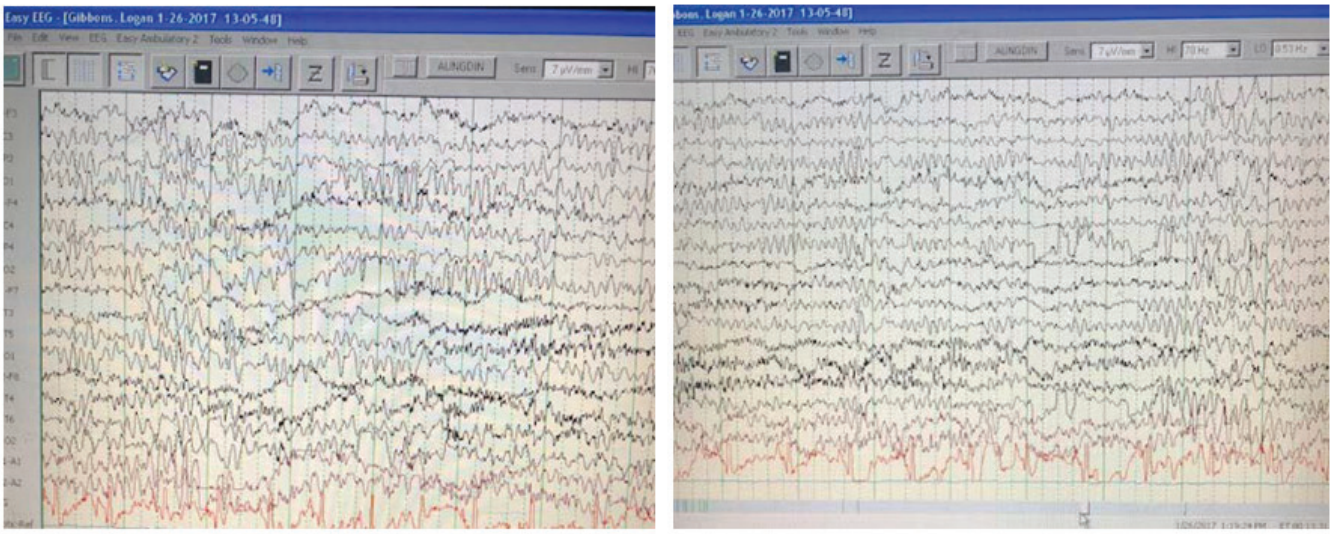
TABLE 1

- Seizures & Epilepsy*
- Encephalopathy, including lethargy, attentional problems, cognition*
- Spasticity*
- Weakness
- Pain, including radiculopathy and neuropathy
- Numbness & tingling
- Anxiety & other mood disorders*
- Hypertension & autonomic dysfunction
- Parkinson's disease & tremors
- Insomnia*
- Bell's palsy & facial nerve dysfunction
- Trigeminal neuralgia
- Hemi-facial spasms, nervous tics/Tourette's*
- Autism/Asperger's*
- Attention deficit disorder & hyper activity*
- Social isolation*
- Occipital neuralgia
- TMJ dysfunction-related symptoms
- Cognitive problems, learning, memory disturbance*
- Headaches: migraine & tension
- Peripheral neuropathy
- Fibromyalgia

*** Potential signs & symptoms of autism**

Direct Effects™ CBD-Treated Conditions* in Clinical Practice (Data from initial 88 patients, now over 600)

FIGURE 7



Jan. 2017 Baseline EEG

as cutaneous receptor activation and nerve conduction times to the CNS in individuals do not vary appreciably. However, with systemic delivery, there exist individual variations in GI transit and absorption, cardiac function, blood flow, and metabolic factors.

For brain disorders, as are encountered in ASD, the critical area of topical drug application is at back of the neck at the hairline (BONATH™). This is the same when treating seizures, headaches, mood disorders, attentional issues, nervous tics/Tourette's, and other CNS-derived symptoms. At BONATH, one can readily access Trigeminal and Vagal Nerve afferent networks through NeuroDirect Effects Technology topical drug application (Figure 6).[5-8]

CLINICAL RESULTS OF NEURODIRECT EFFECTS TOPICAL CBD CREAM IN AUTISM

40 Patients With Autism Spectrum Disorder (Age 2 to 25 Years) Were Seen Consecutively at Outpatient Neurology Clinic

- All had abnormal baseline EEGs; 60% with epileptiform characteristics
- 30% of patients had history of seizures and were currently on anticonvulsants

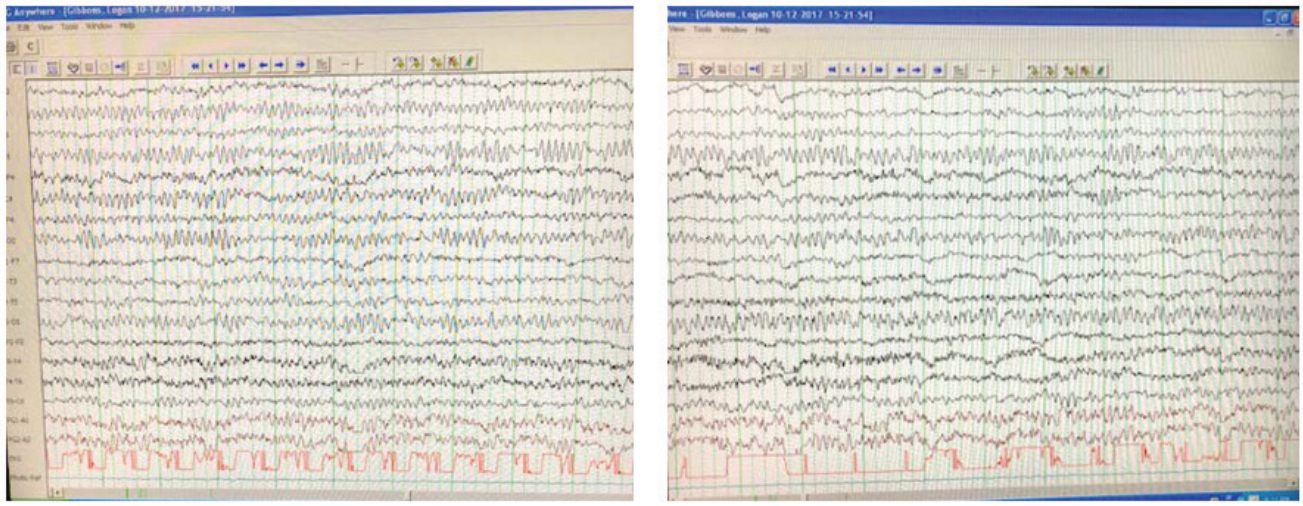
Continuous EEG recording was performed pre- and post-CBD topical drug application at BONATH:

- All baseline EEGs showed varying degrees of improvement within 5 minutes of NeuroDirect Effects CBD cream application at BONATH.
- Over 85% of patients showed improvement in clinical symptoms and behavior within 8 to 10 minutes after CBD
- Patients continued therapy long-term, 2 to 3 times per day, with persistent benefit, often with ability to reduce or completely taper off prior pharmaceutical agents

The advantage of using CBD is that it capitalizes on the body's own ECS, and as such, modulates brain neurochemical and electrical functions that are likely not functioning optimally in ASD. Accordingly, it targets the root causes of symptoms, rather than just treating or covering them up. Table 1 shows varying symptoms that may be helped by the neuro-modulatory effects of NeuroDirect CBD, many of which are observed in ASD. Commonly encountered side effects of current systemic symptomatic treatments of ASD include the following:

- Excessive weight gain from neuroleptics, further diminishing self-esteem, increasing social isolation
- CNS stimulants for attentional problems contribute to agitation, anger outbursts, poor appetite, and insomnia
- Benzodiazepines can cause lethargy, cognitive blunting, dependency, and have potential for withdrawal phenomena, including seizures
- Systemic antidepressants may alter brain neurochemistry and cause receptor up-regulation in developing brains with unknown long-term effects.

FIGURE 8



Oct. 2017 Follow-Up EEG: Normal

CASE STUDY OF ASD PATIENT WITH SEIZURES TREATED WITH NEURODIRECT EFFECTS TECHNOLOGY CBD

Logan G. (15-Year-Old Male With Autism & Seizures)

- Seizures began age 2 after DPT vaccination, described as atypical absence, complex partial, and generalized
- Tried Dilantin, Phenobarbital, Depakote without benefit; Topamax worked, but side effects were intolerable
- For past 10 years, on Keppra 500 twice daily with persistent staring spells, memory lapses, twitching, and automatisms; also experiencing mood disorder with episodes of agitation and social withdrawal
- Nov. 2016: in 9th grade at special needs school of 300 students, not doing well
- Recommended anti-depressants. Parents refused and wanted to try CBD

Jan. 2017: First visit. EEG: Moderate abnormal with episodic bursts high amplitude sharp theta waves. Background improved after NeuroDirect CBD cream application.

- Started on topical NeuroDirect Effects CBD: 30 mg 3x/day and weaned off Keppra
- Follow-up at 3 months: No seizures, doing well in school, more sociable and out-going, less anxious

Follow up Oct. 2017: EEG: Normal and seizure free > 6 months.

- Obtained driver's permit
- Feb. 2018: On only Direct Effects CBD cream 50 mg 2x/day. Made Honor Roll in 11th grade in mainstream HS of 2000 students
- Last visit he was outgoing, confident, engaging, giving eye contact

End Result: Mother states "He's now a normal boy…"

CONCLUSION & SUMMARY

While there is no cure for ASD, intensive, early treatment can make a difference in the lives of many affected children, providing opportunity to lead productive lives. NeuroDirect Effects Technology CBD is particularly attractive in this population as it utilizes the body's own ECS. In utilizing a non-systemic therapeutic mechanism, there is less likelihood for long-term negative effects in developing brains of children.

Inadequately treated, diagnosis of autism is associated with doubled risk for a variety of substance use-related problems, including drugs and alcohol. Between 19% and 30% of individuals diagnosed with autism present with comorbid substance use-related problems. One of the risk factors for substance abuse among this population is diagnosis of ADHD, which frequently co-occurs with autism spectrum disorder. In a recent report published in Journal of Autism and Developmental Disorders, investigators noted diagnosis of ASD is associated with doubled risk for a variety of substance use-related problems. ◆

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BIOGRAPHY

Dr. Ronald Aung-Din practices General Neurology & Neuro-Psychiatry in Sarasota, FL. He is board-certified by the American Board of Psychiatry & Neurology and a member of the American Academy of Neurology. After earning Bachelor's and Master's degrees in Engineering at Bucknell and Cornell, he then attended Columbia University for Premedical studies; followed by Medical School at the University of Texas Southwestern Medical School. Residencies in Neurosurgery and Neurology were at University of Florida. He has participated in over 60 pharmaceutical industry-sponsored clinical trials, functioning as Principal Investigator in drug research studies in MS, epilepsy, pain, Parkinson's disease, and other neurological diseases. He is also active in treating varied neurological and psychiatric conditions using delivery of CNS-active drugs with Neuro-Direct Technology™, developed by him for which 10 US and foreign patents have been granted; with others pending. Publications using this novel therapy in migraine, Parkinson's disease, and diabetic neuropathy; in addition to articles on the use of cannabidiol, CBD, and the non-cannabis cannabinoid receptor agonist, caryophyllene, have appeared in Drug Development & Delivery. He founded AfGin Pharma, LLC (afginpharma.com) in 2009 to advance the technology and its goal of Enhanced Neuro-Therapeutics through Direct Effects Topical Technology.

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Misconceptions, Advantages & Limitations About an Emerging Drug Delivery System

By: Srinivasan Shanmugam, PhD

INTRODUCTION

At their most basic, oral thin films (OTFs) are polymeric films intended to deliver therapeutic moieties either locally or systemically in the oral cavity or through gastrointestinal absorption. OTFs are an attractive option for drug delivery because of the advantages they offer, such as dosing flexibility and ease of administration. They are also fast-acting and can prompt drugs to enter the circulatory system directly by oromucosal and/or sublingual absorption. This avoids exposing drugs to the harsh conditions of the stomach, enabling this drug delivery system to deliver a larger proportion of active compound per dose.

Although OTFs have been available as a drug delivery system since the 1970s, their popularity has soared in recent years due to improved dosing capabilities, packaging, and film stability.[1] In addition, there is growing demand from patients with trouble swallowing tablets and capsules, now thought to be 37% of the population.[2] As a relatively new form of drug delivery, there are currently only about 10 OTF medications on the market, none of which are generic (Table 1).[3] Despite their small number, these OTFs treat a wide range of diseases and disorders, such as migraine, schizophrenia, opioid dependence, pain, nausea, and vomiting. Considering this novel drug delivery system's success, more drugs to treat a larger range of disease indications are likely to be adapted to oral thin films in the future.

TABLE 1

COMMERCIALIZED ORAL THIN FILM PRODUCTS

Brand name	Type of formulation	Application
Zolmitriptan Rapidfilm®	Zolmitriptan oral disintegrating films (ODF)	Migraine
Setofilm®	Ondansetron ODF	Nausea
KP106	D-amphetamine ODF	ADHD
Onsolis™	Fentanyl buccal soluble films	Breakthrough pain (cancer)
RapidFilm®	Ondansetron and donepezil ODF	Nausea; psychosis
Triaminic Thin Strips	Phenylephrine and diphenhydramine ODF	Cough and cold
Suboxone®	Buprenorphine and naloxone (sublingual film)	Opiod dependance
Pedia-Lax™Quick Dissolve Strip	Sennosides ODF	Constipation
Gas-X Thin Strips	Simethicone (sublingual film)	Bloating and gas
Sudafed PE quick dissolve strips	Phenylephrine ODF	Cough and cold

Children, the elderly, and those experiencing nausea often have trouble swallowing, and therefore stand to benefit most from drugs delivered via OTFs. Notably, the growing size of the elderly population, caused by an increase in human life expectancy, is predicted to drive the growth of the OTF market.[4,5] Because the elderly are more prone to chronic illness, the demand for safe and trouble-free drug delivery methods will only increase.

Due to advancements in the science behind OTF design, as well as the predicted increase in OTF market valuation, this drug delivery system is becoming more popular. Few companies have a thorough understanding of the advantages this novel drug delivery system has to offer, and few drug developers have proficiency in the methods needed to optimize OTF drug development and overcome the limitations of OTF manufacturing. Based on my experience working at Avomeen developing drugs in various delivery sys-


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tems, and my expertise working with OTFs, I will provide a thorough review of the formulation and production of OTFs as well as misconceptions, advantages, and limitations of designing and producing them.

OTF OVERVIEW

OTFs come in two major categories: oromucosal and orodispersible. Oromucosal films are placed either onto or under the tongue, or on the inside of the cheek. As mucoadhesives, they are designed to adhere to the inside of the oral cavity and release drugs slowly across the mucous membrane (ie, under the tongue or through cheek) directly into a patient's systemic circulation. For this reason, oromucosal films are particularly fast acting, in addition to avoidance of both first-pass metabolism and degradation in the stomach's acidic environment.

In contrast, orodispersible films are non-mucoadhesive and are designed to break down immediately upon contact with saliva. There are two kinds of orodispersible films: "orally disintegrating" and "orally dissolving." Both types immediately disintegrate in the mouth, but dissolve in different areas of the body. Orally disintegrating films, which tend to be poorly water-soluble drugs, disintegrate in the mouth and then are both dissolved and absorbed in the gastrointestinal (GI) tract. In contrast, orally dissolving films are generally water soluble and therefore disintegrate and dissolve simultaneously in the mouth. Drugs carried by orally dissolving films are absorbed partially in the mouth but mostly in the GI tract.

FORMULATION & PRODUCTION

OTF formulation is based on criteria significantly distinct from that indicated for tablets and capsules. OTF formulation has more limitations than formulation of tablets and capsules. Tablets and capsules can be large or small, solid, or gelatinous. They can also carry additives that enhance stability and solubility. On the other hand, OTF formulation must be designed with the knowledge that the end product will be a small polymeric film. OTFs require unique considerations of dimension and thickness of the film, drug/polymer ratio, viscosity, flexibility, and tensile strength. In addition to basic physical qualities, formulation decisions for OTFs are also tailored to a drug's physiochemical properties, the drug amount needed, and the OTF release type desired.

Films can be characterized in more detail based on a wide range of organoleptic, mechanical, and performance attributes. Organoleptic attributes include qualities that appeal to the senses, such as size, transparency, color, and taste. These qualities do not affect a drug's performance but can affect the patient's acceptance of the OTF. Mechanical properties, such as elongation at break, tear resistance, and folding endurance, are of vital importance to the manufacturing process, as well as to the patient's handling and transportation of the OTF. These properties vary from film to film based on the specific composition. Finally, performance attributes, such as an OTF's uniformity, impurity, and disintegration/dissolution rates would indicate how a drug will perform *in vivo*. In addition to performance testing, drug content uniformity, purity, and stability evaluation are critical during development and manufacturing process. OTF manufacturing can be achieved through a variety of methods, with solvent casting and hot metal extrusion being some of the most widely used; however, many of these methods call for harmful solvents. For this reason, a new method called aqueous slurry casting is gaining in popularity, as it does not require the use of such chemicals.

MISCONCEPTIONS

One of the most common misunderstandings about OTFs is the difference between disintegration and dissolution. By definition, dissolution occurs when a drug goes into solution (eg, in saliva), whereas disintegration occurs when a film breaks into pieces that disperse in the oral cavity for easier swallowing. Another common misconception is that OTFs can only carry aqueous soluble drugs. On the contrary, recent work has demonstrated the incorporation of poorly water- soluble BCS Class II/IV drugs into orally disintegrating films that dissolve in the GI tract.[6-9] In contrast, aqueous soluble drugs of class BCS I/III are incorporated into films with relative ease. These tend to disintegrate and dissolve simultaneously in the oral cavity. Thus, the solubility of a drug dictates its performance, including where it in the body it will dissolve.

ADVANTAGES

The fact that even poorly soluble drugs can be incorporated into OTFs increases their utility as a drug delivery platform, but OTFs' chief advantage is that they are highly patient friendly. OTFs have a much larger surface area than other drug

"Few companies truly have the capabilities and expertise necessary to develop, test, or deliver OTFs. At Avomeen, however, our experience in developing formulations and navigating regulatory systems that oversee OTF drug development prepares us well to navigate this complex landscape. Whereas many developers employ a shotgun technique that requires slower, trial-and-error manufacturing, our company employs a more efficient, targeted technique to choose the components of an OTF based on their chemical properties."

delivery methods, which makes for faster wetting, disintegration, and dissolution. No water, chewing, or swallowing is needed to administer films; saliva is sufficient to disperse or diffuse a drug load. OTFs can also be designed to have a pleasant color and flavor, making them more appealing to young children. OTFs can be thought of as a kind of "precision medication," with perforations in single film that offer both dosing accuracy and flexibility. Dosing flexibility lends itself well to pediatric applications, as children require smaller and more variable dosing than adults, but OTFs may also be attractive to adults who need to take partial doses of medication. Further, those who are receiving medication via OTF will find the films easy to transport and handle.

The final form of OTFs lends them to rapid production, and with the development of powderless, aqueous-based film manufacturing that does not require solvents, manufacturers have the option to produce them around the clock. This process is efficient and takes only two steps of mixing followed by casting, whereas manufacturing tablets and capsules is far more complex. Given their capacity to carry a small load, OTFs are ideal for drugs in development for which production has not yet begun to include large doses. Patent-expiring drugs are also prime candidates to be reformulated for OTF delivery, as the approval of a novel oral film application would entitle these drugs to an additional 3-year period of market exclusivity.

LIMITATIONS

Like any delivery system, OTFs have their own set of limitations. The incorporation of water-insoluble drugs into OTFs is still in its infancy. Tablet and capsules can carry components to help a drug dissolve. In contrast, OTFs are a more streamlined drug delivery system and rely primarily on polymers to increase a drug's solubility. To expand the capabilities of OTF technology, scientists are exploring promising new particle engineering techniques to find new ways to increase solubility of water-insoluble drugs in OTFs.[6-9] Another constraint of OTFs is that they are capable of only carrying a relatively small drug load of about 10 to 20 mgs. Additionally, the larger surface area of an OTF renders it more sensitive to humidity and temperature. Fortunately, special packaging can preserve OTFs in a range of conditions.

Another challenge in OTF manufacturing is testing OTF characteristics. The US Pharmacopeia has not designated any official methods or monographs to test properties, such as mucoadhesion, disintegration, or dissolution. For instance, one reason is that scientists cannot agree on when strips are fully dissolved, the endpoint of some OTF dissolution tests. It is therefore not always straightforward to decide what tests will best assesses a particular OTF product, or how to interpret test results. Unfortunately, it is impossible to draw guidance on optimizing OTF testing from the USP-prescribed disintegration and dissolution tests designed for tablets and capsules. These drug delivery systems vary significantly from OTFs, primarily because of their variance in dosage forms and endpoint determination. However, at Avomeen, we have experience with the development of numerous novel drug delivery systems, including OTFs, and are well-versed in tactics to overcome the challenges and unknowns associated with

manufacturing these items.[10] Our science-based approach systematically selects for OTF components based on their combined chemical properties.

One final testing challenge is that the standard, non-biological methods don't adequately capture the film's or drug's behavior *in vivo*. Water or biorelevant media used in testing does not perfectly mimic the oral cavity's saliva and does not accurately simulate the mechanical stress from the tongue and palate. Dissolution testing procedures need to reflect the varied amounts of saliva present in each patient's mouth. As the ability to incorporate more poorly soluble micro- and nano-particles into OTFs grows, many dissolution tests have been found to be inadequate. While USP IV, which uses a flow-through cell dissolution apparatus, currently has superior discriminating power in this arena, additional methods may further expand our ability to test insoluble drugs carried by OTFs.[12]

Few companies truly have the capabilities and expertise necessary to develop, test, or deliver OTFs. At Avomeen, however, our experience in developing formulations and navigating regulatory systems that oversee OTF drug development prepares us well to navigate this complex landscape. Whereas many developers employ a shotgun technique that requires slower, trial-and-error manufacturing, our company employs a more efficient, targeted technique to choose the components of an OTF based on their chemical properties.

SUMMARY

OTFs are a novel drug delivery system that offers many advantages over more traditional delivery methods like tablets, capsules, and syrups. Market Research Future predicts that the global market for oral thin films will expand significantly from 2018-2023 at a compound annual growth rate (CAGR) of 10.50%.[5] For comparison, another source predicts that the global market value of all novel drug delivery systems, including OTFs, will grow at a more modest CAGR of 2.9% over the same time.[12]

The limitations associated with this method are in large part a result of the newness of OTFs use in drug development. As more drugs are developed or re-adapted to OTF form, solutions addressing these limitations will naturally arise. Although some factors are static — such as the amount of drug a film can accommodate — we do not think of these as limitations, but rather as attributes that cater preferentially to specific populations of patients. Children and the elderly are prime targets for OTF use. Further research will expand the potential applications for OTFs, enabling this novel drug delivery system to become a standard dosage form for all pharmaceuticals.◆

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BIOGRAPHY

Dr. Srinivasan Shanmugam is Technical Director & Head Formulation R&D & CTM Manufacturing at Avomeen Analytical Services. He has more than 15 years of experience on design and development of conventional, NDDS/alternate advanced/modified drug delivery systems, and platform technologies and has successfully designed, developed, and implemented various platform technologies to enhance oral bioavailability of highly hydrophilic as well as poorly soluble/bioavailable highly lipophilic drugs. Dr. Shanmugam has managed many global product development collaborations with big pharma, has published numerous research articles in prestigious pharmaceutical sciences journals, presented more than 20 of his work in various symposiums/conferences globally, and is a reviewer and editorial member of various journals. He earned his PhD in Pharmaceutical Sciences at Yeungnam University.

Special Feature

Excipients: Matching Ingredients to Molecules Improves Functionality

By: Cindy H. Dubin, Contributor

The pharmaceutical excipients market is projected to reach $9.7 billion by 2025, up from $6.9 billion in 2019.[1] Industry experts point to advancements in functional excipients, the emergence of multifunctional excipients and co-processed excipients, as well as an increase in biopharmaceuticals and the rising adoption of orphan drugs as the reasons behind this expected growth. Fillers and diluents have accounted for the largest share of the excipients market, mainly because of their increased use in solid oral drugs and manufacturing advantages. And while not surprising that oral formulations comprise the largest segment of the excipients market, topical formulations are estimated to be the fastest growing sector.

In this exclusive *Drug Development & Delivery* magazine annual report, excipient manufacturers describe how their excipient offerings are improving drug release, solubility, taste, physical characteristics, viscosity, and more, for a range of molecules.

ABITEC: Functional Lipid Excipients Combine for Enhanced Solubility

CBD is an emerging therapeutic field employing CBD as an agonist at various CBD receptors in the endogenous human cannabinoid system. Difficulties in the per-oral dosing of CBD include low aqueous solubility and a very high rate and extent of first pass metabolism.

ABITEC's functional lipids have helped numerous manufacturers in the CBD industry overcome these challenges, explains John Tillotson, RPh, PhD, Pharmaceutical Technical Business Director, ABITEC. The company's functional caprylic and caprylic/capric tri-glycerides solubilize large amounts of CBD isolate, up to as much as 40% w/w. Additionally, incorporation of CBD dissolved in MCT with mono- and di-glyceride emulsifiers and surfactants generates a self-emulsifying delivery system carrying CBD. Certain long-chain lipids can be incorporated in these systems to promote lymphatic transport of CBD, allowing a portion of the dose to avoid first pass metabolism.

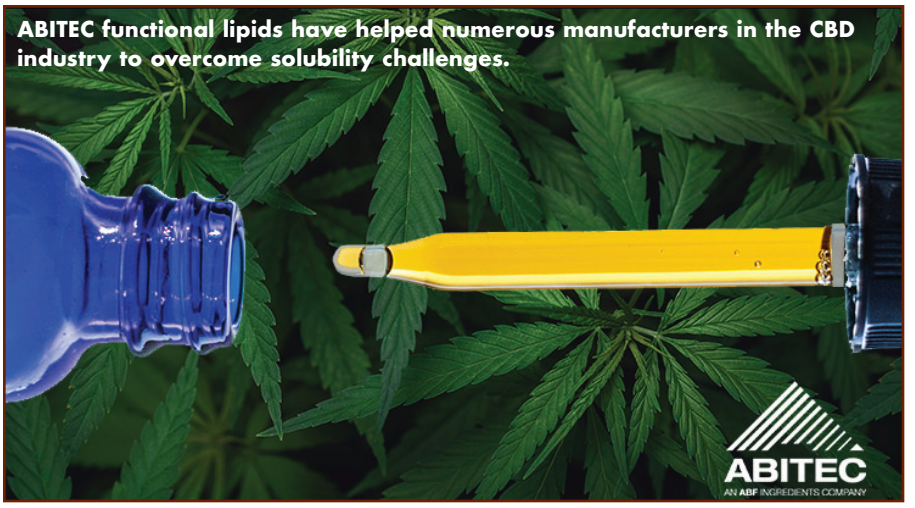
"ABITEC's lipid technologies have been successful at formulating numerous CBD-based products, improving both active delivery and solubility in per-oral dosage forms," he says.

Additionally, ABITEC's functional lipid excipients such as CAPMUL®, ACCONON®, and CAPTEX® are utilized in combination with one another to enhance the solubility and emulsification properties of topical and transdermal products. ABITEC's excipients provide improved transdermal penetration of actives, increased active solubilization, and enhanced emulsification in creams and gels.

The pharmaceutical industry is increasingly employing specialized excipients, or co-processed excipient systems, in order to realize the finished dosage form's critical quality attributes. The synergistic combination of multiple excipients to formulate additional excipient systems with expanded capabilities increases the market offering and leads to an overall market expansion for excipients.

ABITEC manufactures numerous multifunctional excipients, including Sterotex® NF, which serves simultaneously as a direct-compression tablet lubricant and a direct compression tablet binder and CAPMUL GMO-50 EP/NF, which can act in topical formulations as both an oil-in-water emulsifier and as a transdermal penetration enhancer. Additionally, ABITEC's CAPTEX, CAPMUL, and ACCONON ingredients can be synergistically employed in self-emulsifying formulations with multiple routes of administration and differentiated functionalities.

galenIQ™ is a filler binder that provides a sweet taste to tablets and chewables (BENEO/©Dima Sobko; Shutterstock).



ABITEC functional lipids have helped numerous manufacturers in the CBD industry to overcome solubility challenges.

"The role for multi-functional and co-processed excipients systems is expansive and includes a multitude of applications, including increased compaction characteristics, improved flowability of powder, more rapid dissolution and disintegration characteristics, rapid oral disintegration with improved organoleptic characteristics, generating crystalline to amorphous changes, and increasing API solubility and lymphatic transport," says Dr. Tillotson. "Ultimately, combinations of excipients and multi-functional excipients will play an ever-expanding role in the formulation of emerging therapies, which require a broader spectrum of excipient performance attributes."

Ashland Life Science: Excipients That Enable Efficacy, Integrity, & Usability

Multi-functional or co-processed excipients are effective and efficient ways to improve the manufacturing process of a drug product. Benefits of using these excipients include enhanced productivity, reduced operating cost, and improved product quality. For example, Ashland's Benecel™ DC HPMC is a co-processed excipient with superior flow properties and improved compressibility, making it an ideal polymer to use in high-speed tableting operations or continuous manufacturing, explains Deneen Law, Global Marketing Director, Pharmaceutical Specialties, Ashland Life Science.

Ashland offers excipients for oral solid, oral liquid, and parenteral dosage forms. Key products include: Benecel HPMC, Klucel™ HPC, Viatel™ bioresorbable polymers, Plasdone™ povidone and copovidone, and Polyplasdone™ crospovidone. "These products help formulators increase the solubility of poorly soluble APIs, control drug release of modified-release products, reduce tablet size while maintaining API load and tablet integrity, reduce disintegration time of tablets, and enhance processability," she says.

Plasdone S630 Ultra is a new grade of copovidone designed for use in hot-melt extrusion (HME) due to its improved stability, powder flowability, and thermal processability. One customer's formulation contained an API that is oxidation labile, so processing with high temperatures and high shear forces normally associated with HME would accelerate its instability, explains Ms. Law. "Plasdone S630 Ultra copovidone enabled our customer to complete the late-stage development of their formulation, which required using HME."


Ashland brings the magic of controlled release with Benecel™ XR HPMC controlled-release matrix formers.

Another customer was having problems related to low tablet hardness and productivity. Ms. Law says Benecel K100M XR HPMC is an improved HPMC with enhanced compactability properties compared to a standard controlled-release grade of HPMC. "When the client used Benecel K100M XR HPMC, they were able to not only obtain higher tablet hardness, but also increase the speed of the tablet press therefore, improving productivity."

Avantor: Improving Stability & Viscosity of Parenteral Formulations

Increasing growth of novel treatments and biosimilars are driving the need for excipients that are suitable to be used in injectable and parenteral formulations. Parenteral excipients require stringent control of elemental impurities, bacterial endotoxins, and bacterial loads in addition to their specific chemical impurity levels and functional attributes. In some cases, excipients can increase the drug product stability period while decreasing attributes such as viscosity or injection site pain and inflammation.

One of the major concerns for biologic drugs is stability and decreasing viscosity of the formulations. As a supplier of critical materials to the biopharmaceutical industry, Avantor has provided excipients

with controlled levels of reactive and elemental impurities to improve the stability and viscosity of formulations. Benzyl alcohol, propylene glycol, detergents such as polysorbate, and Triton X 100 with lower levels of reactive impurities such as aldehyde, are a few examples. "The decreased potential of these materials to react or interfere with drug products increases formulation viability and stability period, leading to longer useful life of the finished drug product," says Nandu Deorkar, Vice President, Research & Development – Bioprocessing, Avantor.

Avantor has also developed a multifunctional excipient-based formulation platform to reduce viscosity of high concentration monoclonal antibody (mAb) formulations. "In these cases, we can utilize a combination of select novel excipients to reduce viscosity while increasing stability of the formulation," Dr. Deorkar explains.

Avantor offers a variety of functional excipients that can be used in parenteral, oral delivery, and implantable device formulations. Under its J.T.Baker® brand of high-purity cGMP chemicals, Avantor's range includes amino acids, antimicrobials, buffers and salts; detergents for solubilization and stabilization of parenteral or liquid formulations; and multifunctional, co-processed, and specialty excipients offered with reduced levels of elemental impurities or reactive impurities, such as aldehydes and ketones.

BASF Pharma Solutions: Addressing Physicochemical Challenges of Monoclonal Antibodies

Pharmaceutical excipients are growing on two main fronts. First, is growth associated with increased access to medicine. Specifically, the "Pharmerging" regions of the world have a growing middle class and increasingly robust health care systems, which includes the distribution of pharmaceuticals, and by default, excipients. Second, in the more developed regions, work is focused on the next generation of pharmaceuticals, many of which will be complex dosage forms and large-molecule biologics, which typically require a higher degree of specificity and are tailored to meet a certain challenge (e.g. protein stability). As the prevalence of large-molecule formulations continue to grow, so does the need for innovative excipients to meet these challenges.

"The development of excipients in the biologics space are interesting and uniquely challenging for both suppliers and formulators," says Dr. Frank Romanski, Head of Global Marketing – Pharma Solutions, BASF Pharma Solutions. "In the upstream cell culture space, dozens, if not hundreds, of ingredients are utilized within the media, and each must be carefully selected and maintained for cell viability. Unfortunately, with the large pool of ingredients, it can be extremely complicated to determine the root cause of lower cell viability. However, within the formulation space, more traditional surfactants, buffers, salts, and other excipients (less overall) are utilized within parenteral dosage forms, but now the drug is no longer a simple and readily predictable small molecule, but rather something far more complex like a monoclonal antibody, where countless interactions, impurities, and other physicochemical challenges need to be carefully studied and addressed to ensure stability and efficacy."

To that end, BASF Pharma Solutions, together with Roche, publicly collaborated to develop Kolliphor® P188 Bio, a fit-for-purpose ingredient utilized as a shear protectant in CHO cells for the production of numerous biologic drugs. Kolliphor P188 Bio functions by forming a pseudo-coating over the CHO cells during growth and prevents them from a premature death associated with process shear (e.g. bubble bursts), a well-known and publicized problem in mammalian cell culture.

"This product mitigates the risk associated with other surfactants, where trace species can contribute to massive declines in cell viability during production," says Dr. Romanski.

BASF Pharma Solutions' excipient portfolio covers a multitude of functionality in five core areas: instant and modified release (solid oral dose), solubilization, softgels, skin delivery, and biologics. In addition to Kolliphor P188 Bio, BASF's recent excipients include Soluplus®, Kollicoat®, Smartseal, and Kolliphor HS 15, the latter currently being studied for use in protein stabilization. Most recently, BASF has also launched a series of digital tools to assist formulators, regulators, and purchasers in the pharma industry through its ZoomLab™, RegXcellence™, and MyProductWorld software applications.

BENEO: Technical Functionality That Tastes Better

Fillers and diluents account for the largest excipient segment because tablets are still the most common and popular form of taking medicine, says Dr. Michael Black, Head of Sales Pharma, BENEO. It is in this area that BENEO offers galenIQ™, a water-soluble filler binder with a pleasant, sweet taste used to make tablets, chewables, effervescents, lozenges, and powder dispersions such as sachets and stick-packs. galenIQ, which is Isomalt (EP, USP-NF, JP), is a disaccharide

alcohol and polyol derived from beet sugar. It is available in eight specific grades, and can also improve the palatability of oral dosage forms.

galenIQ proved helpful for a customer that wanted to make a tablet with three separate plant extracts. Each extract was difficult to compress as one was very hard and dense, another one was very soft, and the third one was oily. And all three had an unpleasant bitter taste, explains Dr. Black.

"By mixing and compressing with galenIQ, the customer was able to make a robust tablet with a pleasant neutral taste," he says.

The galenIQ range is multi-functional, comprising different grades of solubility with varying particle size. "Multi-functional excipients and co-processed excipients are of major interest to formulation developers because they can reduce the complexity of formulation design and enable robust formulations that are suitable for efficient manufacturing processes, such as high-speed tableting and continuous manufacturing," explains Dr. Black.

Cambrex: Overcoming Challenges of High-Potency, Low-Dose Drugs

High-potency drug substance development has been a core focus in the industry, but the highly potent nature of the substances makes manufacturing containment and safety critical throughout the manufacturing process. When high-potency drug substances are used in the formulation of low-dose drug products, there are development challenges along the way to becoming a final drug product.

"Manufacturing containment remains a consideration when formulating low-dose drug products," says Rich Shook, Director, Drug Product Technical Services and Business Integration, Cambrex. "The core focus is on segregation, content uniformity, and balancing the physical and chemical characteristics of the drug substance into a drug product. Proper excipient selection and evaluation of the critical physical parameters of those excipients is paramount to the successful development of the final dosage form."

Manufacturing techniques for low-dose drug products are also important. Although wet granulation and roller compaction are effective manufacturing methods, direct blending (for encapsulation and compression) is more effective at decreasing manufacturing complexity and cost, he says. Excipient development plays a large role in enabling direct blend implementation. "Innovations in excipient manufacturing such as spray drying and co-processing of excipients has helped alleviate some of the challenges in low-dose drug development," says Mr. Shook. "Regardless of the excipient(s) being used, an evaluation of Critical Material Attributes (CMAs) is essential to properly match the excipients to the targeted drug substance and is critical to the success of a directly blended formulation."

Multiple synergistic excipients can be combined into one particle (usually by way of spray drying or resin loading), resulting in a co-processed excipient. The co-processed excipients offer increased functionality and performance when compared to the standalone excipients, he says. Co-processed excipients can be modified based on established CMAs and dependent upon the targeted drug substance in the formulation. The particle size and ratio of excipients can be modified, which he says is advantageous when used in a direct blended formulation.

"At Cambrex, we have extensive expertise with drug substances targeted at low doses, using best-in-class development and manufacturing approaches to bring them together with excipients in finished drug products," says Mr. Shook. "We work to overcome challenges faced for direct blended, low-dosage forms to ensure that safe, efficacious end products are brought to the market."

Croda: Tailoring Excipient Selection to a Desired Function

As diseases and conditions become more complex, they warrant solutions that are more complex. With this increase in complexity comes the need to solve challenges of stability, delivery, and bioavailability. Consider proteins, for example. A complex structure with exposed functional groups allows for a number of side reactions to potentially take place, whether that be oxidation, carbonylation, or deamidation. Breakdown of the structure could cause issues with drug and/or formulation stability as well as drug absorption and efficacy. To combat this, excipients are used as stabilizers, emulsifiers, preservatives, or delivery enhancing agents. This ensures that complex drugs perform as they should.

"The key word here is functional," says Arsalan Khan, Technical Marketing Coordinator, Croda. "Excipients are no longer thought of as fillers or just a material to bulk out a formulation. They are specialized ingredients, and selected to help with a specific effect, whether that be targeting delivery of the drug, aesthetics of the final formulation, or shelf life of the final drug product."

Mr. Khan says Biopharma has been one of the biggest drivers here. "Common concerns like drug stabilization, surface adsorption, or agglomeration are real issues, and it is important that an appropri-

ate ingredient is selected to help prevent these issues from occurring."

Co-processed excipients also serve an important purpose in the discussion of functional excipients. When selected properly, co-processed or multi-functional excipients enable one ingredient to serve multiple purposes. "Croda's Super Refined™ Polysorbate 80 is an example of this, serving as a stabilizer for complex protein structures and preventing surface adsorption of proteins to various surfaces, such as the end container of a final formulation, says Sreejit Menon, PhD, Research and Technology Manager, Croda. "One of the main drivers behind co-processing is enhancing the effect that either excipient can provide solely, such as drug absorption and/or permeation."

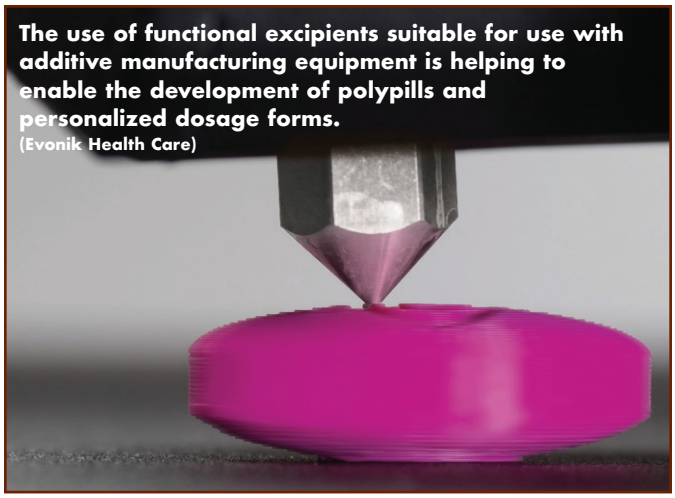
Ingredient purity comes into play, as the level of functionality can, in many cases, be a direct function of the impurity levels. Dr. Sreejit says: "Croda's high-purity ingredients, such as Super Refined™ Polysorbate 80 or Super Refined™ PEG 400 are used with many APIs in various dosage forms and have shown improved stability versus when formulated using standard grade versions of these excipients. Therefore, it's important to take all considerations of an excipient into account in its selection to ensure it not only does the job it's supposed to, but does it at the highest possible level."

Daicel Corp.: Two Co-Processed Excipients for Orally Disintegrating Tablets

Oral administration remains the most popular route of administration, however, from the viewpoint of medication adherence, conventional formulations for oral administration, such as tablets and capsules, inflict difficulties in swallowing to patients with dysphagia. Orally disintegrating tablets (ODTs) have been developed for such patients and increase adherence. A widely used method for producing ODTs is direct compression (DC).

To provide improved flow properties and compressibility, various DC excipients have been developed including co-processed excipients, which are blends containing mainly fillers, binders, and disintegrants. These blends are processed by a variety of technologies, such as melt granulation, dry granulation, wet granulation, fluid bed granulation, and spray drying.

According to Dr. Yukiko Suganuma, New Business Development, Pharma Solutions, Daicel has developed two co-processed excipients for ODTs: GRANFILLER-D and HiSORAD. "GRANFILLER-D has three advantages," says Dr. Suganuma. "First, it is well balanced between tablet hardness and disintegration time



The use of functional excipients suitable for use with additive manufacturing equipment is helping to enable the development of polypills and personalized dosage forms.
(Evonik Health Care)

and enables ODTs with rapid disintegration under high tablet hardness. Second, it has a high API dosing capacity. Even with API, tablets prepared with GRANFILLER-D have wicking ability and disintegrate rapidly. Third, GRANFILLER-D shows good content uniformity of content because it mixes well with API. The reason for this is assumed to be that its nonspherical and irregular-shaped particles contribute to the maintenance of homogeneous conditions."

In December 2019, Daicel launched HiSORAD as a new co-processed excipient for ODTs. Similar to GRANFILLER-D, HiSorad is well balanced between tablet hardness and disintegration time, says Dr. Suganuma. "The most distinct attribute of HiSORAD is its excellent compactibility. It is expected to be suitable for poorly compressible APIs."

Evonik Health Care: Functional Excipients to Enable, Enhance, & Differentiate Complex Dosage Forms

The development of more specialized and personalized drug products is driving pharmaceutical demand for functional excipients that can optimize safety and performance while increasing levels of patient acceptability. Functional excipients can be leveraged across a range of oral and parenteral dosage forms to match virtually any target release profile. They are also vital in enhancing the solubility of poorly soluble drugs, enabling the modified release of microbiota, and effectively targeting specific sites such as the colon.

There is also growing demand for oral functional excipients that can be used with additive manufacturing technologies to accelerate clinical trials, create individualized dosing profiles, or combine several APIs into a single polypill utilizing additive manufacturing technologies.

"Pharmaceutical companies have recognized that multi-func-

tional excipients are a highly versatile option to boost innovation outcomes during the development of complex drug products," says Paul Spencer, Head of Pharmaceutical Polymers and Services for Evonik Health Care. "However, it's essential that they partner with industry specialists in this field to help them anticipate and address likely formulation obstacles that would otherwise increase cost and regulatory risk, and delay the path to market."

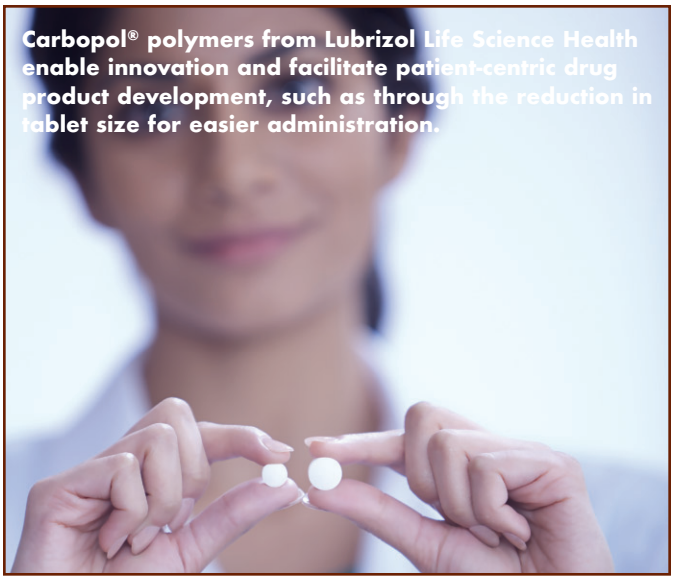
Evonik's EUDRAGIT® polymers are multi-functional excipients suited to address requirements such as film formation for immediate- or modified-release coatings, binding in granulation processes, drug solubilization in spray-drying and melt extrusion, or matrix formation for sustained release tablets. Functional excipients such as EUDRAGIT and RESOMER® medical device polymers can also help to reduce formulation complexity, time for QC testing, and overall regulatory risk, he says.

"We continue to develop functional excipient solutions that can address unmet market needs," Mr. Spencer says. "For example, our new proprietary Advanced Excipient Manufacturing Process technology has allowed us to combine the respective benefits of two existing monographed polymers to create EUDRAGIT® FL 30 D-55. This new combination polymer for enteric coatings enables the design of highly flexible and easy-to-process enteric coatings that are attractive for use with dosage forms such as multiparticulate tablets."

Lubrizol Life Science Health: Polymers Impart Critical Properties

Multifunctional excipients are increasingly important as formulation requirements have become progressively more demanding. Many APIs in development today are complex and come with bioavailability or solubility issues, making excipients that can address multiple needs crucial. In liquids and semisolids, an excipient that can impart rheology modification, suspending ability, improved stability, and optimal sensory properties is highly coveted.

There is also an uptick in the development of orphan therapies, precision medicines, and 505(b)(2)s, all of which have unique formulation considerations and can require specialized inactive ingredients. "For oral dosage forms, inactive ingredients that have both controlled-release and binding properties can reduce tablet size and ensure better patient compliance," says Elena Draganoiu, PhD, Global Technology Manager, Lubrizol Life Science (LLS) Health. Additional functionalities such as bioadhesive properties, taste masking, if appropriate, and being already listed on the FDA's inactive ingredient database (IID) provide even more value.



Carbopol® polymers from Lubrizol Life Science Health enable innovation and facilitate patient-centric drug product development, such as through the reduction in tablet size for easier administration.

LLS Health's Carbopol® polymers are one example of an excipient that meets these criteria and is IID-listed for select dosage forms and use levels. The company's excipient portfolio also includes Noveon® polycarbophil, Pemulen™ polymers, and Pathway™ thermoplastic polyurethane for the pharmaceutical (prescription and over-the-counter), nutraceutical, and drug-eluting device markets.

"Many of our excipients are listed on the FDA's IID for these routes of administration at specific maximum potencies per unit dose," says Dr. Draganoiu. "Additionally, LLS Health polymers can impart multiple critical properties, including rheology modification, optimal suspension and stability, ideal sensory properties, bioadhesion, tablet size reduction, taste masking, and controlled drug release with tablet size reduction."

Clients come to LLS Health with specific formulation or product challenges, such as bitter-tasting drugs, adhesion requirements to a biological membrane, or viscosity-control needs for no-spill pediatric formulations. LLS Health recently assisted a client with reducing the size of an oral solid formulation for diabetes treatment, as too-large tablets can cause patient compliance issues, especially in geriatric patients, she explains. "Tablet size reduction is one of the multiple functionalities our Carbopol polymers can instill to a formulation, along with extended drug release, taste masking, and processing flexibility, as these excipients are compatible with multiple manufacturing methods, such direct compression, roller compaction, and wet or dry granulation." ◆

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Drug Development
EXECUTIVE

Doug Drysdale

President & CEO

Tedor Pharma, Inc.

Tedor Pharma, Inc.: A Strategy Shift to Serve Both Generic & Branded Companies

The pharmaceutical contract development and manufacturing organization (CDMO) outsourcing market was valued at $150.66 billion in 2019 and is expected to reach $246.24 billion by 2025.[1] Tedor Pharma, Inc.'s niche in this growing CDMO market has been as a full-service provider focused on generic drugs for 19 years. However, that business model shifted in the past couple years when Doug Drysdale took the helm as President and CEO. He previously served as Chairman and CEO of Pernix Therapeutics and CEO of Alvogen, Inc. When he joined Cumberland, RI-based Tedor, he made it a point to extend the CDMO's services and capabilities to branded drug companies. That shift in business model has resulted in a significant increase in Tedor's branded business in 2019.

The foundation for this shift in business model began with a multi-million dollar expansion of Tedor's manufacturing capabilities, which included the installation of new multi-purpose cGMP manufacturing suites. Then, in May 2018, Tedor recapitalized and reorganized its business funded by DORA Ventures, Inc., which was created to invest in under-valued healthcare assets and related segments. DORA is owned and controlled by Drysdale and Tedor Chairwoman Laura Iorio.

This past June, Tedor announced a partnership with Altus Formulation as the exclusive North American licensee and provider of FLEXITAB technology, which produces breakable extended-release tablets that are being positioned as a cost-effective differentiator in the market for branded products. To date, three FLEXITAB products have been approved in 25 countries.

Drysdale recently spoke with *Drug Development & Delivery* about FLEXITAB technology, his strategy for managing a shift in business model, and how Tedor is addressing the needs of small- and medium-size companies developing innovative and repurposed small molecules for unmet medical needs.

Q: Since becoming CEO in May 2018, what have been your top priorities?

A: Three things: people, processes, and building a growth engine. People are our first priority. I believe Jim Collins said it well. It's about getting the right people on the bus. And getting those people in the key seats on the bus before you start to drive where you're going. So, throughout the past couple of years, we've built a very strong, well-aligned team with a focus on quality systems and technical product development capabilities. In terms of processes, I'd say any business that's been around for 19 years has things that can be done more efficiently. We focused on removing low value, unnecessary tasks and replacing paper with technology and having our people spend more time on value-added activities and creating more capacity within the current organization we have before having to expand. Then in terms of building a growth engine, there are a lot of sales and marketing fundamentals we put in place in 2018-19, and as we enter 2020, we've expanded our business development head count threefold, added telesales capabilities, and significantly increased our digital efforts to drive new opportunities our way. Technology provides a huge opportunity to reach out to prospective new customers.

Q: What are these new opportunities?

A: We were somewhat unknown among the branded company audience. We've used our 19-year track record, our personal networks, and the growth engine to attract small- and medium-size branded clients throughout the past year. Those clients are thrilled with our customer service and our technical ability to find solutions to their product development challenges. We wouldn't have been able to do that if we didn't combine the growth engine and the expanded technical capabilities to put our money where our mouth is.

Q: Can you tell our readers about the decision behind Tedor's shift in strategy from a predominantly generic model to a branded and generic CMDO model?

A: It's been about shifting the talent base within the company. The company historically has a generic background, and we wanted to diversify the business and bring in more branded clients. It's not just about manufacturing generic drugs but branded medicines as well. We've also shifted away from co-developing drugs to becoming a full-fledged CDMO. In that role, we didn't want to compete with our customers. To that end, we divested our interest in a number of ANDAs that we owned and co-owned, and we've added new customers, both branded and generic, and provided greater revenue diversity going forward. In that shift, we've focued on bringing in talent to broaden our formulation and development services.

Q: What, if any, challenge(s) does this pose and how are you addressing them?

A: It hasn't posed any major issues. If anything, it's provided opportunities. We've expanded our formulation and development teams, bringing in new talent and expanded the breadth of those development services. For our generic clients, the focus is often on finding a non-infringing path to market as fast as possible, and we've been doing that for 19 years. But for our branded clients, it's more about finding solutions to the physical limitations of their molecules, like overcoming challenges to solubility or bioavailability. So, there is a different mindset between those two types of customers. That stretches the team, but it's also very rewarding. On the new product side, we have more potential solutions available to us.

Q: What type and size of pharma company does your new strategy best suit?

A: Small- and medium-size generic and branded companies. Some have their own in-house development, many do not. For some of our branded customers, their pipelines consist of just a handful of products or less, and each product is very important to them. As medicine becomes more personalized and targeted, the annual volumes of these products are getting smaller, certainly smaller than the blockbusters we've seen in the past. So, these companies want to partner with a CDMO that's the right size for them where they won't get lost or deprioritized, where the service is personal, and where every one of their products is important to us.

Q: Can you point to a specific client you recently helped with your services: the problem they had and how you solved it?

A: It's great when a company comes to you with a challenge and you are able to solve it. There was a small US Biopharma company that selected Tedor to manufacture their first branded product for clinical trials. That put an awful lot of trust in us. Following the completion of the Phase 1 trial, the client decided to change the API manufacturing site and the process. This was done to reduce the impurities of the API from the original source. That change in API source led to differences in the physical properties of the API. It meant that during our trials with the API, the tablet showed lamination and capping as compared to the original formulation. We had to figure out how to solve that. We ran a number of R&D experiments to see if a change in excipients could resolve the issue, but from the client's point of view, that wasn't ideal. The product was already dosed in a Phase 1 study, and the customer didn't want to change the formulation significantly. We evaluated a couple of different approaches, such as non-aqueous wet granulation, adding a small amount of binder while keeping the formulation excipients at the same level. That worked well and resulted in an acceptable formulation. We also looked at compaction, which we explored to avoid the addition of new excipients. The challenge we had there is that the amount of API that was available to us was limited. That is often the case with new molecules. We ran a slugging trial on a compression machine and this also led to an acceptable formulation. So, we were able to avoid adding new excipients and significantly changing the formulation through this process. So those two alternative process approaches were shared with the client, and the client will decide which way they want to go before we go into Phase 1b and Phase 2.

Q: Can you describe the FLEXITAB technology and the value it offers to your branded clients?

A: FLEXITAB is one tool in our toolbox. It centers around a patented excipient that enables us to produce breakable extended-release tablets. That may not sound that remarkable on the face of it, but it's not normal. Typical extended-release tablets shouldn't be broken by patients because that impacts the release of the drug. With FLEXITAB, patients can break a 20mg tablet into four pieces, and each will retain the integrity of a 5mg extended-release tablet. It's quite a breakthrough. This enables easy titration for products in which dosing needs to be gradually increased by the physician. It enables flexible dosing with fewer SKUs because you can mix and match to fill in dose strengths between the pre-compressed tablets strengths. And it helps with easy swallowing for children and the elderly because you can break the tablet into "fours" without affecting the extended-release capabilities. For our clients, it offers IP protection to 2037, so when they are thinking about developing an extended life cycle for existing products but still bring value, this helps protect those brands for several years.

Q: Can you provide any details about FLEXITAB products already approved, such as their therapeutic targets and their market potential?

A: The first one was a tramadol once-a-day approved in 25 countries. There is also a 24-hour trazadone formulation and a 12-hour tramadol APAP combination that was approved in the EU. This technology has been through both the EU and US regulatory processes and can be used across a number of different indications. I believe a particularly interesting use is where titration is needed early on, such as for pain or CNS disorders, or as anti-depressants and anti-epileptics, where physicians want to be careful about increasing the dose gradually in the beginning. The potential going forward is unlimited by the imagination of the companies with which we work.

Q: What advice can you offer to other CEOs who may be going through a shift in business model?

A: I've launched a few start-ups and managed a couple of turnarounds, and the most common experience is that the path to success always looks very different than the original plan you make at the outset. It's a winding road rather than a straight road. Stick to your vision, continue to believe in where you are going, and be the standard bearer. But be open to adjust along the way to achieve the overall strategy. ◆

Reference

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NATURAL LANGUAGE PROCESSING

How Life Sciences Companies Are Leveraging NLP From Molecule to Market

By: Jane Z. Reed, PhD, MA

INTRODUCTION

Finding the right flavor of artificial intelligence to bring value to your organization is fraught with obstacles: what tool to use, what vendor to partner with, what application will most benefit from AI? One type of AI has already been bringing active value to pharma and healthcare organizations for a couple of decades – natural language processing (NLP) for text analytics. NLP text mining can be used to extract the key information from unstructured text, rapidly and effectively, to provide decision support from molecule to market. The following discusses some of the challenges facing pharma researchers and executives; the benefit NLP can bring; and some specific customer-use cases (covering patent landscaping, gene-disease associations, access to safety silos, and more).

CHALLENGES IN LIFE SCIENCE ORGANIZATIONS FOR ACCESS TO UNSTRUCTURED DATA

In the life sciences industry's pipeline from drug discovery through development and into delivery, insight is needed at every stage, to answer questions, get through gates, or achieve milestones.

For example, early on in target discovery, researchers need to search the biomedical literature for specific genes involved in their therapeutic area of interest. Alternatively, they might want to search patent literature to understand the landscape around specific technologies, or to understand the competitive whitespace for certain disease targets. Or perhaps pharmaceutical executives want to find the optimal sites for a Phase 1 or Phase 3 clinical study; or might want to know more about patient-reported-outcomes for a particular product by searching Twitter, or voice of the customer feeds.

Answers to all these questions support business and healthcare decisions, and it is imperative that pharmaceutical companies employ the best possible view of data to generate insights. However, up to 80% of healthcare data is stored in an unstructured format, making it difficult to access and analyze, which often prevents scientists, researchers, and clinicians from leveraging the best possible information when making decisions.

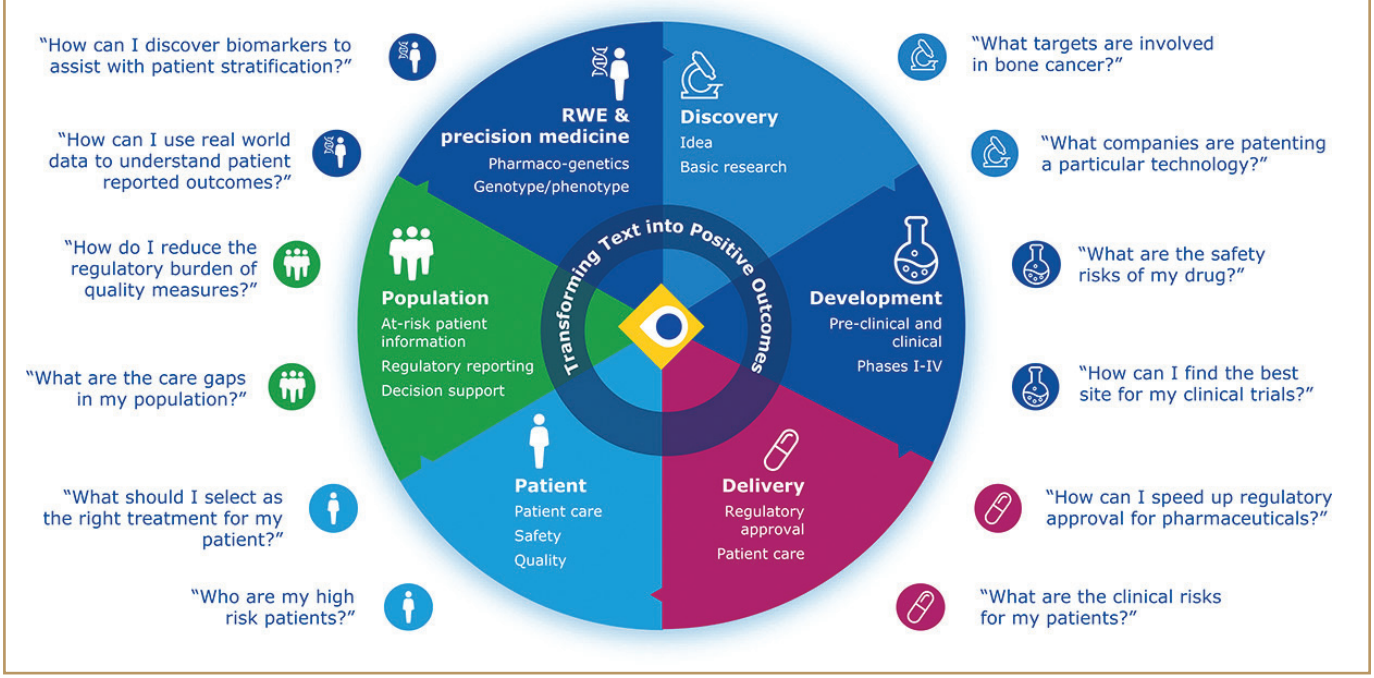
To overcome the limitations of unstructured data, many of the leading life sciences companies have turned to natural language processing-based text mining. Among the key benefits of text mining with NLP is that, unlike standard keyword search that retrieves documents based on keywords that users must then read, NLP in essence reads the documents for users and identifies relevant facts and relationships. NLP extracts those facts and relationships in a structured format that enables review and fast analysis, connecting facts to synthesize knowledge and create actionable insights.

WHY NLP FOR TEXT MINING?

Historically, researchers have had little choice but to manually wade through free text, reading documents and creating summaries and analyses on their own. However, as the volume of healthcare data increases both in substance and format, this approach has become less viable. As a result, researchers need text analytics tools to make sense of this vast amount of information, and to uncover key facts and relationships that can provide answers to their questions.

NLP-based text analysis consists of several processes, includ-

FIGURE 1



ing information retrieval, information extraction, lexical and semantic analysis, pattern recognition, tagging and annotation, and data mining techniques, such as association analysis and visualization. The overarching goal is, essentially, to turn text into data for analysis and insights, via application of NLP and analytical methods.

NLP enables a mapping from words in textual data and documents to meaning in a structured format for actionable decision support. NLP understands the grammar of a sentence and can identify nouns, verbs, the start and end of phrases and sentences, and more.

A key concept associated with text mining is ontologies, which are used to categorize similar things, group them together, and provide synonyms for concepts. For example, cancer, carcinoma, and neoplasm all refer to the same concept, so grouping this data together enables researchers to generate much more comprehensive data searches.

NLP-based text mining can be used across virtually any type of textual document, whether it's scientific literature, patient literature, internal safety reports, drug labels, clinical trial data, social media, or electronic health records. By using NLP, researchers can transform their decision-making: from a document-centric view of finding documents and reading them, to a data-centric view of uncovering new insights from previously hidden relationships.

From molecule to market, life sciences companies have used NLP-based text mining to transform texts for decision support in multiple areas, including gene disease mapping, target selection, biomarker discovery or safety, right through to post-market activities, such as pharmacovigilance and competitive intelligence. The six use cases further on will give a flavor of these applications and the benefits NLP brings.

REAL-WORLD PHARMA USE CASES OF NLP

Pfizer: Effective Search for Patent Landscaping & Competitive Intelligence

Patent literature can provide a valuable competitive edge for pharmaceutical researchers by providing the first mention of critical data for novel drug targets, novel chemicals, compounds, and where competitors are working in specific disease areas. The problem is that patent literature documents are notoriously hard to search, often using obtuse and confusing language.

Pfizer observed that doing manual review and search of patents to find targets being researched by competitors in three therapeutic areas would require 50 full-time-equivalent days – a significant amount of manual effort. In response, Pfizer leveraged NLP text mining to build an automatic workflow to extract four main entities: target, indication, invention type, and organization. This data set is updated weekly across three of the major patent

registries (WIPO, USPTO, EPO). The weekly data uploads go into a database that has a visual interface for business intelligence. The workflow improved recall tenfold over what Pfizer achieved with manual review, and the precision is equally strong.

Pfizer found that this integrated, automatic process significantly reduced the resources required to keep researchers and decision-makers up-to-date, and, also significantly increased the comprehensiveness of the data they were reviewing. Further, because the dashboards are so easy to interpret, the solution decreases the time to new insights, and broadens the value of patent data across the team.

Sanofi: Text Mining for HLA Allele Disease Associations

Sanofi has a significant focus on multiple sclerosis. In one project, Sanofi researchers sought to better understand what biomarkers might be useful in precision medicine research; so wanted to annotate the output of next-generation sequence (NGS) pipelines with the most up-to-date information from the literature. Particularly, they wanted to find any associations possible between HLA alleles and haplotypes and autoimmune diseases.

To address this, Sanofi employed NLP to mine literature sources to find HLA alleles and haplotypes and their relationships with diseases and drug sensitivity. They developed a suite of NLP queries that identified a wide range of HLA alleles, relationships, and diseases from abstracts or full-text articles. This strategy enabled the team to quickly find over 50 associations; both 22 associations already highlighted in a key review paper and an additional 33 disease- and drug-sensitivity associations from across the literature landscape that hadn't been curated. NLP enabled the Sanofi team to standardize the information for integration into an internal knowledge base with a dashboard for broad use across the entire team. This provides Sanofi with a broader and more comprehensive knowledge base from which they can now confidently explore potential new biomarkers.

Merck: Preclinical Safety Data From Documentum Study Reports

Safety assessment during drug discovery through clinical development and into post-market surveillance and pharmacovigilance is essential. At all stages, project teams need the most comprehensive view of relevant data – ideally, both internal and external.

Pharma and biotech companies spend hundreds of thousands of dollars on preclinical safety studies, but the final reports often are stored in secure document repositories that are not easy to search, making it difficult for researchers to access the high-value information in these legacy documents. To capture key findings from safety assessment reports, Merck's Safety Assessment and Laboratory Animals Resources (SALAR) group created an NLP workflow to extract key information from their safety report repository held in Documentum.

New reports are added to Documentum on a regular basis, and Merck's NLP workflow analyzes them to pull out metadata on species, study duration, compounds, and other information. Notably, this workflow focuses on the interpreted results sections of these reports because it is the portion that includes expert conclusions on histopathology findings and adverse events, as distinct from any mentions of these in other sections (eg, methodology sections).

These new insights have enabled Merck to alleviate concerns in instances in which preclinical observations have been found not to be human-relevant, and also impacted on reducing late-stage failure. By better understanding the context of broad historical data, the company can better assess its current, active pipeline.

Eli Lilly: Mining ClinicalTrials.gov for Clinical Trial Intelligence

A number of life sciences companies employ NLP text mining to uncover information from clinical trials databases, such as ClinicalTrials.gov, TrialTrove, or Pharma Projects. Though these pipeline databases often store valuable information, it is difficult to query the unstructured text in those documents or use ontologies for better search and recall.

NLP helps researchers rapidly identify, extract, synthesize, and analyze relevant information such as clinical trial site, selection criteria, study characteristics, patient numbers, and characteristics that would not be possible using other approaches.

Eli Lilly's competitive intelligence clinical group needed to assess the landscape of Phase 1 and 2 clinical trials that were testing two or three drugs in combination for autoimmune diseases. Manually, they had found only seven trials, and had decided this approach required too much effort. However, with a relatively straightforward NLP query over ClinicalTrials.gov, Lilly was able to find an additional 300 trials very quickly. In addition, the NLP query extracted the drug names, specific autoimmune disease, the phase of the trial, and the sponsors; all normalized and structured for rapid effective review.

Novo Nordisk: Actionable Insights From Real-World Data

There's a real buzz right now about real-world data (RWD). In pharma and healthcare, understanding the real-world impact of therapies on patients is critical. RWD can shed light on real-world clinical effectiveness and on safety profiles of products across a broad patient community; as well as to assess patient-reported outcomes and to understand product reputation management. However, many RWD sources contain unstructured text, which prevents easy analysis. Text analytics is essential to unlock the value from sources of RWD, such as social media, EHRs, clinical guidelines, and customer call transcripts.

Novo Nordisk wanted to identify healthcare market trends and detect patterns from three disparate RWD sources: call center feeds, medical information requests, and conversations with healthcare providers. The company was already analyzing this data, but via an inefficient and labor-intensive process in which vendors did manual extraction and scanning.

To solve the problem, Novo Nordisk built an NLP workflow to transform RWD from the three sources to drive a medical and patient dashboard, making medical and patient data actionable across its global workforce. Novo Nordisk hosts this information in an Amazon Web Services data lake, running NLP queries to pull out key topics and trends, and providing visual dashboards using Tableau.

The new workflow replaced the need for manual scanning, saving the company approximately two full-time employees per year. Novo Nordisk also reduced spend on external vendor report generation, has automated evidence-based insights generation, and significantly broadened access to these insights across its team.

Bristol-Myers Squibb: Text Mining EMRs for Patient Stratification of Heart Failure Risk

All pharmaceutical companies have a strong interest in understanding how different therapies and drugs are being used and applied. More specifically, Bristol-Myers Squibb (BMS) wanted to understand more about patient stratification for heart failure risk. Heart failure patients typically exhibit high levels of clinical heterogeneity, which is problematic for treatment and for risk stratification. BMS researches believed that if they could acquire a deeper understanding of the clinical characteristics of these patients, they could potentially understand how best to treat different patients or populations.

To that end, researchers obtained electronic health record and imaging data for about 900 patients, and used NLP to write queries, extract and normalize approximately 40 different variables around patient demographics, clinical outcomes, clinical phenotypes, and other variables such as ejection fraction and left ventricular mass.

With advanced statistical clustering, BMS researchers identified four classes of patients with discrete clinical and echocardiographic characteristics that showed significant differences in 1- and 2-year mortality and also 1-year hospitalizations. By better understanding how to stratify patient populations for heart failure, BMS has unlocked insights on that can potentially improve the design of clinical trials, identify unmet needs, and develop better therapeutics.

DRIVING COMMERCIAL EXCELLENCE THROUGH DATA TRANSFORMATION & ANALYTICS

At every stage of the drug development pipeline from molecule to market, data can provide the competitive advantage that determines the difference between success and failure. The problem for many pharmaceutical companies is that 80% of that data is unstructured and difficult to access and investigate for insights.

NLP-based text mining unlocks the hidden value in data sources as disparate as patents, scientific reports, patient literature, electronic health records, customer call transcripts, and social media. For life sciences companies, higher quality data means improved gene disease mapping, target selection, biomarker discovery, and competitive intelligence – boosting pharmaceutical innovation and enhancing commercial value.◆

BIOGRAPHY

Dr. Jane Reed is Director, Life Sciences at Linguamatics, an IQVIA company. She is responsible for developing the strategic vision for Linguamatics' growing product portfolio and business development in the life science domain. Dr. Reed has extensive experience in life sciences informatics, having worked for more than 15 years in vendor companies supplying data products, data integration and analysis, and consultancy to pharma and biotech, including roles at Instem, BioWisdom, Incyte, and Hexagen. She earned her PhD in Physiology from the University of Birmingham and her MA in Natural Sciences from the University of Cambridge.

DEVELOPMENT TIMELINES

Drug Development Times, What it Takes - Part 3

By: Josef Bossart, PhD

INTRODUCTION

This is the third and final article analyzing the Development and Review Times of the US FDA's new drug approvals (NDA and BLA) for the period 2010 through 2018. The first article[1] provided an overview of development and review times while the second article[2] looked at New Molecular Entity (NME) product approvals. This article looks at the development and review times associated with the larger and much more mixed group of products based on Previously Approved Actives (PAA).

PREVIOUSLY APPROVED ACTIVE APPROVALS

NDA approvals for products incorporating PAA are assigned NDA Classification Codes[3] by the FDA. Table 1 summarizes the products available for Development and/or Review Time analysis. Unfortunately, not all approved products can be analyzed because of missing or redacted information in the FDA's published review documents. None of the products in this analysis are Abbreviated New Drug Approvals (ANDA).

All PAA products are categorized as 505(b)(1) or 505(b)(2) approvals. A 505(b)(1) submission requires the sponsor to have complete rights of reference to the underlying active ingredient. This is generally the case when the filing is from the originator or a licensee. A 505(b)(2) submission does not have the same rights of reference to the previously approved pharmaceutical active. A total of 149 PAA products were 505(b)(1) approvals, the balance were 505(b)(2) approvals.

REVIEW TIMES

The Review Time analysis includes 545 PAA products. Mean and median Review Time averages by Type are presented in Table 2 (Categories with less than 20 approvals are excluded).

A quick review of the Review Times summarized in Table 2 suggests there is little difference between the median Review Times for Previously Approved Active and New Molecular Entity products. There is a difference in the mean Review Times of about half a year in favor of NME approvals that may reflect the greater regulatory experience of companies developing NME products. There is little reason to believe that the regulatory review hurdles and timelines for PAA products should be greater than for NME products, although NME products are more likely to receive some sort of accelerated review. That the shorter Review Times are related to regulatory expertise is suggested by the one-third year difference in the median review times for PAA products that were approved through the 505(b)(1) or 505(b)(2) process. The PAA 505(b)(1) approvals are more likely to be associated with companies that originally developed the active. Review delays were noted in the approval documents for 28% of the 505(b)(1) and 43% of 505(b)(2) filings, further suggesting the greater regulatory experience of

TABLE 1

Type	Short Description	Number of Products
Type 2	New Active Ingredient	9
Type 2,4	New Active Ingredient in Combination	1
Type 3	New Dosage Form	210
Type 3,4	New Dosage Form in Combination	9
Type 4	New Combination	67
Type 5	New Formulation	222
Type 7	Previously Unapproved Active	24
Tentative Approvals		7
Total		**549**

Previously Approved Active Approvals Available for Analysis (2010-2018)

"**Development Time** is the elapsed time between the earliest of either: Pre-IND Meeting, first IND filing, or the start of the first human clinical trial and the filing of an NDA or BLA. **Review Time** is the time that has elapsed between the first submission of a new drug filing, an NDA or BLA, and the date the product is granted first approval by the FDA."

companies submitting 505(b)(1) applications.

DEVELOPMENT TIMES

The figures in Table 3 reveal the considerable difference in Development Time between NME- and PAA-based products of 3.5 years or more (mean and median). The median values perhaps best represent the most realistic benchmark regarding the time spent in the clinical stage of development for a product using a Previously Approved Active. While there is limited opportunity to significantly shorten the clinical development process, there is a seemingly unlimited opportunity to extend it.

The mean average and median Development Times for PAA product approvals are remarkably consistent as a function of Type. The exception is found with Type 4 Combination Products that have required about a year less. This may simply be a function of relatively more Type 4 products (41%) being developed and approved on the basis of bioequivalence programs.

The figures in Table 4 suggest why, on average, Development Times for New Molecular Entity products are much greater than Previously Approved Active products. While NME approvals require full efficacy and safety studies, PAA products can be approved on the basis of more limited efficacy and safety studies, or even just bioequivalence studies.

TABLE 2

Type	Mean	Median
All PAA (n=545)	1.8 Years	1.0 Years
Type 3 (n=209)	1.7 Years	1.0 Years
Type 4 (n=67)	1.5 Years	0.9 Years
Type 5 (n=220)	1.7 Years	0.9 Years
Type 7 (n=24)	1.3 Years	0.8 Years
505(b)(1) (n=149)	1.5 Years	0.8 Years
505(b)(2) (n=396)	1.7 Years	1.1 Years
All Approvals (n=802)[1]	1.5 Years	0.9 Years
All NME (n=340)[2]	1.3 Years	0.8 Years

PAA and NME Mean and Median Product Review Times (2010-2018)

TABLE 3

Type	Mean	Median
All PAA (n=387)	5.1 Years	4.2 Years
Type 3 (n=186)	5.1 Years	4.3 Years
Type 4 (n=54)	4.2 Years	3.7 Years
Type 5 (n=129)	5.2 Years	4.2 Years
505(b)(1) (n=135)	4.9 Years	3.9 Years
505(b)(2) (n=252)	5.2 Years	4.3 Years
All Approvals (n=802)[1]	6.7 Years	5.6 Years
All NME (n=340)[2]	8.8 Years	7.7 Years

PAA and NME Mean and Median Product Development Times (2010-2018)

TABLE 4

Type	Efficacy/Safety Trials			Bioequivalence Trials		
	N	Mean	Median	N	Mean	Median
All PAA	265	6.0 Years	5.1 Years	122	3.0 Years	2.6 Years
Type 3	126	6.1 Years	5.2 Years	60	2.9 Years	2.3 Years
Type 4	32	5.2 Years	4.6 Years	22	2.9 Years	3.2 Years
Type 5	96	5.8 Years	4.7 Years	33	3.4 Years	2.6 Years
All 505(b)(1)	97	5.5 Years	4.5 Years	38	3.3 Years	3.1 Years
All 505(b)(2)	168	6.4 Years	5.3 Years	84	2.9 Years	2.3 Years

PAA Development Times as Function of Development Program

TABLE 5

Development Program	Development Time	Review Time	Total Time
New Molecular Entity[2]	7.7 Years	0.8 Years	8.9 Years
Previously Approved Active			
- Efficacy/Safety Trials	5.1 Years	1.0 Years	6.1 Years
- Bioequivalence Trials	2.6 Years	1.0 Years	3.6 Years

Median NME and PAA Development and Review Times (2010-2018)

PAA products approved solely on the basis of bioequivalence data complete the clinical development portion of their development on average in 3 years, with a median of 2.6 years. This is half the 6 (mean) and 5.1 (median) years, respectively, of PAA products developed on the basis of efficacy and safety indicating trials. PAA products approved on the basis of efficacy and safety trials still require about 2.5 years less Development Time than NME products.

The differences noted earlier between 505(b)(1) and 505(b)(2) review times are also seen with clinical development times. 505(b)(1) programs show as much as a one-year shorter Development Time.

PUTTING IT ALL TOGETHER

The numbers paint a rather consistent picture as presented in Table 5 that compiles median Development and Review times for NME and PAA products. The differences matter not only when estimating the overall timeline to complete a clinical development program through to approval, but also when deciding what path to take when developing a Previously Approved Active.

The factors underlining these timelines are not restricted to clinical development competence or bad luck during the development process. Equally important are issues, such as funding gaps that force development pauses, unexpected issues with patient recruitment, or an unexpected difference of opinion with the FDA on trial design and patient numbers.

Clinical development and regulatory plans will always suggest that products can be developed in less time than these averages. Of course they can, but on average they don't. Any company or team suggesting a development program will be completed more quickly than the benchmarks of Table 5 needs to clearly explain how they expect to "beat the averages."

About a year ago, I was speaking to a former colleague about an interesting new product development his small company was working on with a previously approved active for a well understood and established indication. The product offered a clinically interesting twist on the usual treatment paradigm. The product also had positive efficacy data by virtue of earlier investigator IND work. Based on their clinical development plan, which would include efficacy and safety trials, they expected to be submitting their product to the FDA in 2 or 3 years. My immediate response, without reviewing their development plan, was that they were seriously underestimating the timelines. Was I questioning their competence? Of course not, these are top notch folks. Experience suggested that the time would be double or more what they were estimating. Catching up a year later, I was told that a few months after our discussion the FDA had come back with a requirement for more preclinical toxicology data that would delay the program by a year and add in more expenses. I suspect this is only the start of the surprises that will hopefully not delay the program beyond the medians in Table 5. Stuff happens, even to the best.

FINAL THOUGHTS

The Development and Review times presented in these three articles are not the final word. They should be the starting point for discussions and the stress testing of development plans. There are two key questions that need to be asked. How do we plan to beat the averages? What will it cost to achieve this exceptional, average beating, performance?

There are many lessons to be learned in the Product Approval documents available at the FDA website. It takes a bit of work to go through the many documents, but like a good detective story, there are clues that point to important evidence of what happened and why. Understanding how others came to be where they are is an important step in understanding what is ahead of us. "History doesn't repeat itself, but it does rhyme."[4] ◆

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1. https://drug-dev.com/development-timelines-drug-development-times-what-it-takes-part-1/
2. https://drug-dev.com/development-timelines-drug-development-times-what-it-takes-part-2/
3. NDA Classification Codes. https://www.fda.gov/media/94381/download
4. Generally attributed to American humorist Mark Twain (Samuel Clemens.)

BIOGRAPHY

Dr. Josef Bossart serves as Managing Director at The Pharmanumbers Group. He has 4 decades of experience in the biopharmaceutical industry, having held senior sales, marketing, operations, and business development positions within Big Pharma and emerging Specialty Pharma companies. His activities include analyzing corporate, technology, and product development strategies in the area of Drug Delivery. Dr. Bossart earned his PhD in Medicinal Chemistry from The Ohio State University.

MARKET BRIEF

Allergic Rhinitis Immunotherapy: Opportunity Analysis & Forecasts to 2028

By: Rose Joachim, PhD

INTRODUCTION

Allergic rhinitis (AR) is a common inflammatory disease in which an individual reacts to an otherwise innocuous inhaled substance with symptoms including runny nose, sneezing, nasal congestion, and itchiness of the eyes, nose, and palate. In the seven major markets (7MM: US, France, Germany, Italy, Spain, UK, and Japan), the total prevalence of AR is estimated to be 15%-30% of the population — an enormous potential market size.

While a wide variety of over-the-counter (OTC) therapies exist for the temporary abatement of AR symptoms, allergen-specific immunotherapy (ASIT) is the only truly disease-modifying therapy available for AR. This therapy involves the gradual administration of allergens in increasing doses to desensitize patients over time. Although the immunomodulatory effects of ASIT are complex and not fully understood, successful immunotherapy has been linked to a shift from a Th2-skewed immune profile, characteristic of atopic conditions, to a more tolerogenic phenotype. The two most common forms of ASIT used in the treatment of airborne allergens are subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT).

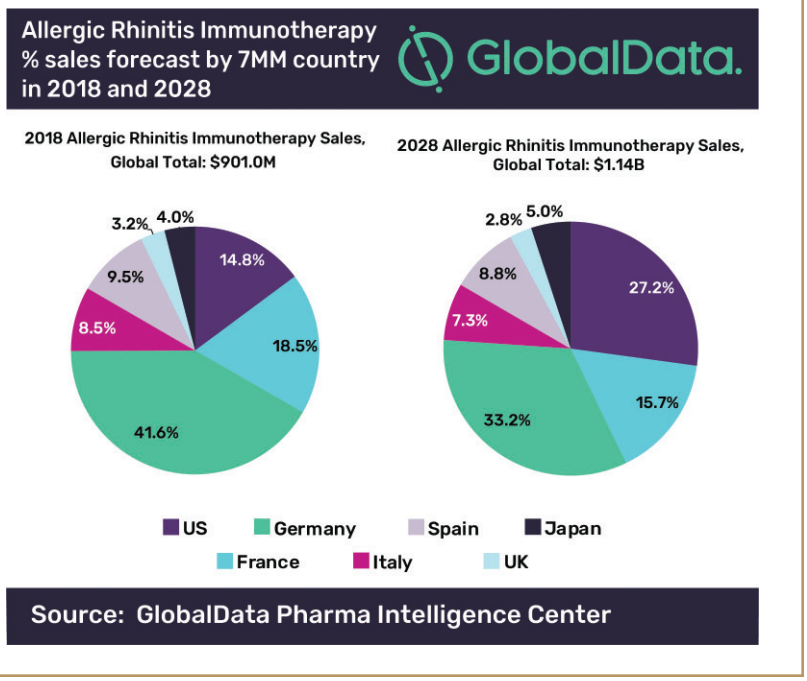
Due to a number of factors, ASIT remains underused in the 7MM, but this may be beginning to change. The field is currently in a state of flux and the resultant changes will likely redefine the market going forward.

ALLERGIC RHINITIS IMMUNOTHERAPY MARKET FORECAST

Between 2018 and 2028, the AR ASIT market is expected to grow at a slow but steady pace. GlobalData estimates 2018 sales to be $901 million across the 7MM. By the end of the forecast period in 2028, sales are expected to increase to $1.1 billion at a compound annual growth rate (CAGR) of 2.3%. Overall, the key factor driving this growth is the anticipated approval and launch of five new pipeline therapies:

- Allergy Therapeutics' Grass MATA MPL
- ASIT Biotech's gp-ASIT
- Biomay's BM-32
- ALK-Abello's Itulazax
- Shionogi and Stallergenes Greer's S-525606/STG-120

FIGURE 1



"Between 2018 and 2028, the AR ASIT market is expected to grow at a slow but steady pace. GlobalData estimates 2018 sales to be $901 million across the 7MM. By the end of the forecast period in 2028, sales are expected to increase to $1.1 billion at a compound annual growth rate (CAGR) of 2.3%. Overall, the key factor driving this growth is the anticipated approval and launch of five new pipeline therapies."

While the first three products target grass pollen allergy using short-course pre-seasonal SCIT, the other two products target allergies toward different groups of trees using SLIT tablets. Despite this global trend toward growth, market dynamics are expected to vary greatly throughout the 7MM, reflecting unique, region-specific current and historical therapeutic trends.

In the five key European Markets (5EU: France, Germany, Italy, Spain, and UK), there is a heightening focus on the use of ASIT products with greater clinical accountability, particularly those with formal marketing authorization (MA). This ongoing shift away from a market dominated by named patient products (NPPs) makes room for new players from the pipeline, such as ASIT Biotech's gp-ASIT, Biomay's BM-32, and ALK-Abello's Itulazax.

However, during the forecast period, GlobalData expects overall growth in this geography to be quite low (CAGR of 0.5%). This attenuated growth despite the launch of several new products is the anticipated result of a large number of NPPs leaving the market as well as the often slow-moving nature of national healthcare services in establishing coverage for ASIT products.

Even after the initial launch of SLIT tablet products several years ago, the US has remained quite resistant to the use of pre-formulated ASIT products, commonly used in Europe. US allergists instead tend to opt for the flexibility of formulating ASIT doses using bulk extracts. However, GlobalData believes that the potential launch of the first ultra-convenient, short-course, pre-seasonal SCIT product, Allergy Therapeutics' Grass MATA MPL (previously known as Pollinex Quattro Grass), during the forecast period could inspire patients, physicians, and payers to utilize new methodologies. Due to an expected modest increase in the use of and new introduction of more costly pre-formulated ASIT products, GlobalData expects that growth will be particularly pronounced in the US, with a CAGR of 8.7%. This includes the expected launch of Grass MATA MPL in 2023, the continued uptake of the recently launched house dust mite (HDM) tablet, Odactra, and the launch of a second HDM tablet, Stallergenes Greer's Actair, in 2020. This last product has been marketed in Japan for several years and is only recently in clinical development for the 5EU and US.

Since the launch of several pre-formulated SLIT products in Japan in 2014, the size of the ASIT market in this country has been steadily growing. The recent launch of Torii's Japanese cedar pollen (JCP) SLIT tablet, Cedarcure, and the expected launch of Shionogi's S-525606, also for the treatment of JCP allergy, is expected to continue to expand the market size potential in Japan. In Japan, strong market growth (CAGR of 4.8%) is expected during the forecast period, associated with the increased use of marketed SLIT tablet products for both HDM and JCP allergies, as well as the launch of a second JCP SLIT tablet product, S-525606, in 2023.

PIPELINE PRODUCTS SEEK TO MAKE ASIT QUICKER & MORE CONVENIENT

Currently, only a small portion of AR patients who are eligible for ASIT will actually be treated. One key factor driving low treatment rates is the inconvenience associated with receiving the therapy over the course of multiple years. In response to this ongoing issue, companies have invested greatly in R&D efforts to create products that act faster, are more effective, and give patients flexibility in their dosing regimen. This effort can plainly be seen in the current AR ASIT pipeline.

To improve the convenience of SCIT, an ongoing trend in the 5EU has been the development of products that require fewer doses and thus fewer visits to the allergy specialist. These products typically consist of allergens specially formulated to be hypoallergenic, thus allowing for the safe injection of higher doses. One example of this type of product seeking MA in the US and EU is Grass MATA MPL, which is an allergoid formulation of 13 grass pollens combined with a microcrystalline tyrosine (MCT) depot and a monophosphoryl lipid A (MPL) adjuvant. The current pipeline also includes SCIT products utilizing other methods to improve efficacy and diminish allergenicity. For example, both ASIT Biotech's gp-ASIT and Biomay's BM-32 use hypoallergenic allergen peptide fragments. However, the products differ in that gp-ASIT uses natural, hydrolyzed peptide fragments from *Lolium perenne* pollen, while

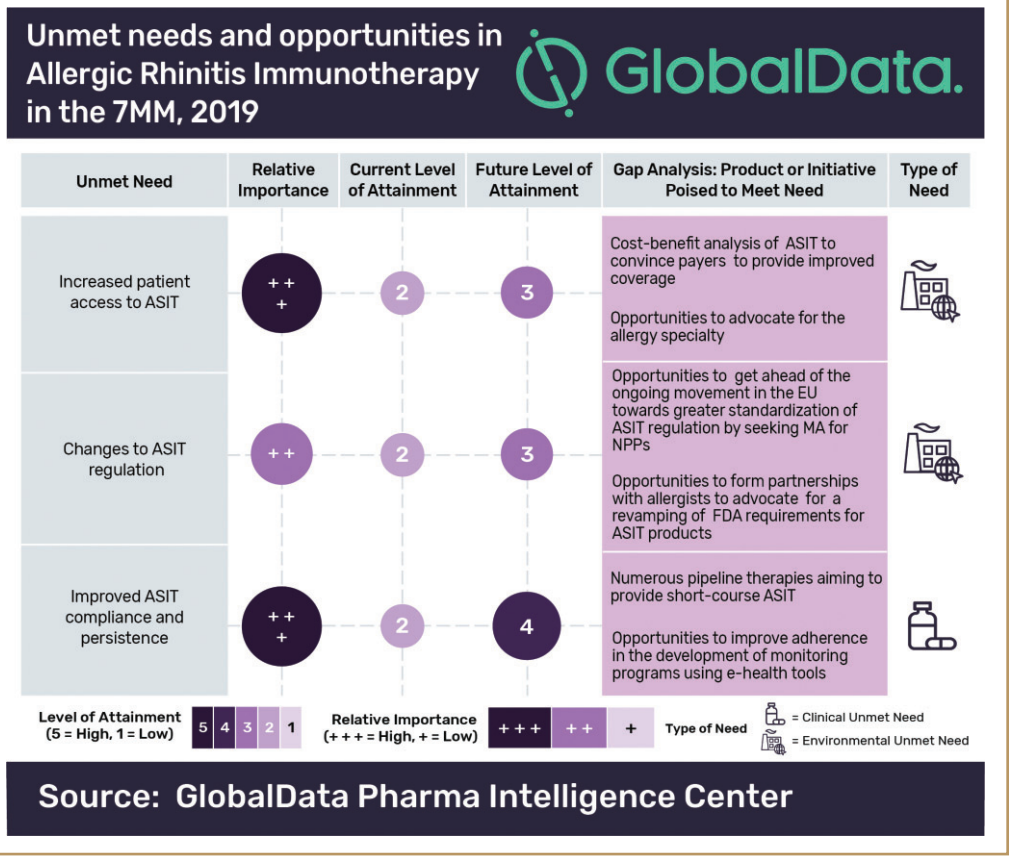
BM-32 uses a fusion protein consisting of recombinant peptides targeting key B-cell epitopes for *Phleum pratense* pollen and an immunogenic carrier protein.

US and 5EU key opinion leaders (KOLs) were especially enthusiastic about these new short-course, pre-seasonal grass pollen SCIT products, particularly Grass MATA MPL and gp-ASIT. They believed that the therapies would be more convenient for patients and that the shortened duration of therapy could improve long-term compliance. However, while US KOLs seemed optimistic about gaining access to these new pre-formulated SCIT products, they also seemed unwilling to completely overhaul the way they administer ASIT. US KOLs believed that the use of bulk allergens would remain the dominant way for ASIT to be administered in the country. They reasoned that bulk allergens can be used to formulate mixtures of allergens for polysensitized patients while new, pre-formulated products only target a single allergen. Additionally, KOLs noted that there was a financial incentive for keeping ASIT methodologies the same: US allergists can charge fees for the formulation of allergen extract mixtures in-house, which provides a substantial source of renewable income for small practices.

Another major strategy to address low treatment rates in the AR ASIT space is to increase the availability and usage of SLIT products. Because of a lessened risk of serious adverse events, SLIT can be self-administered by patients at home. While SLIT drop products have been available for some time in the 5EU, throughout the past decade the SLIT market is steadily being overtaken by SLIT tablets administered once daily. These tablets, mainly developed and marketed by Stallergenes Greer and ALK-Abello, were subjected to rigorous clinical development programs and as a result, have been granted formal MA in multiple countries throughout the 7MM. While these SLIT tablets have been very successful in Japan and the 5EU, their uptake in the US continues to be less than expected. This is mainly due to poor insurance coverage for the products, as well as a continued focus of US allergy specialists on the use of multi-allergen SCIT formulated from bulk allergen extracts. ALK-Abello's Itulazax for birch homologous tree pollen allergy and Shionogi and Stallergenes Greer's S-525606/STG-120 for JCP allergy make use of ALK-Abello's and Stallergenes Greer's tried-and-tested tablet formulations found in products like Grazax and Oralair, respectively.

KOLs from Japan stressed the growing importance of SLIT in their country. Since the introduction of SLIT tablet and drop products for HDM and JCP allergens several years ago, KOLs noted that the use of ASIT was steadily increasing and would likely continue to increase in years to come. KOLs explained that patients were happy with the relief they were getting from these products and the news was quickly spreading by word of mouth. Japanese KOLs also specified that the increased safety profile of SLIT made physicians more willing to introduce the therapy into their practices.

FIGURE 2



UNMET NEEDS STAND AS KEY BARRIERS TO GROWTH

Despite being the only disease-modifying therapy available for the treatment of AR, ASIT remains underused. These low treatment rates severely limit the full potential for growth in this market. KOLs interviewed by GlobalData suggested this is in great part due to a number of lingering unmet needs in the field, standing as barriers to increased uptake. These barriers include inadequate access, a shifting regulatory landscape, and low treatment compliance and persistence.

First, in the US and 5EU, KOLs highlighted cost and inadequate insurance coverage as two of the main issues driving this lack of usage. With effective and inexpensive OTC drugs for AR readily available on the market, KOLs explained that private and public insurance providers are often less willing to pay for ASIT. One KOL from the US believed that if ASIT was made more affordable, it could easily double the number of patients receiving the therapy. KOLs from throughout the 7MM agreed that the financial burden of ASIT was a key factor in stifling patient initiation of ASIT as well as promoting early discontinuation. In the 5EU and Japan, KOLs also linked underutilization of ASIT to inadequate access to allergy specialists who were able and willing to offer the therapy. In the 5EU, KOLs stressed the need for increased funding for allergy specialty training, while in Japan they noted the lack of financial incentives for allergy specialists to offer ASIT in their practices.

KOLs interviewed by GlobalData also noted that the regulations governing the use and development of ASIT products require some significant changes. This sentiment was particularly strong in the 5EU, where unregulated NPPs fill the marketplace. KOLs from the 5EU noted a growing preference both by physicians and governmental authorities for drugs with a formal MA rather than NPPs. This movement towards increased standardization in ASIT product regulation in the EU took root in Germany in 2009 via enactment of the Therapie-Allergene-Verordnung (TAV), which required NPPs for certain key allergens to obtain formal MA within a given time frame. One 5EU KOL noted that those actions have since transformed the German ASIT market, which now focuses heavily on products with MA. 5EU KOLs believed that the rest of the EU was beginning to move in this direction. Although they felt this trend would be good for the market as a whole, they noted that the number of available products would shrink drastically. However, these KOLs argued that by ensuring only the safest and most effective products were available on the market, a stronger ASIT market would take shape in the future.

Finally, KOLs highlighted the need for patient compliance and persistence to improve. There are a variety of known factors affecting patient compliance to ASIT, half of which involve practical considerations such as method of administration, side effects, and cost, while the other half involve more nuanced factors such as the attitude of the patient and relationship with their physician. Along with the potential availability of more convenient, efficacious ASIT products in the future, KOLs noted that improving relationships between patients and their doctors could be a helpful move. For example, patients receiving SCIT tend to demonstrate better compliance in comparison to those receiving SLIT. KOLs explained that this is in large part due to the fact that SCIT requires patients to visit their doctor regularly, an ongoing relationship that likely improves treatment compliance and persistence.

NEW DEVELOPMENTS

Since the publication of GlobalData's report, Allergic Rhinitis Immunotherapy: Opportunity Analysis and Forecasts to 2028, it was announced that the grass pollen SCIT product, gp-ASIT, failed its latest Phase III trial. While the future for this particular product is no longer clear, GlobalData believes that the overall size and trends of the grass pollen ASIT market will remain as projected, with other pipeline grass pollen SCIT products claiming the sales originally anticipated for gp-ASIT. ◆

BIOGRAPHIES

Dr. Rose Joachim is a Senior Healthcare and Pharmaceutical Analyst at GlobalData in Boston. In 2017, she earned her PhD in Biological Sciences in Public Health at Harvard University. Her dissertation research explored the effects of age on immune system function during sepsis. When she wasn't at the bench, she spent her time teaching and developing new science curricula as part of the Science Education and Academic Leadership certificate program at Harvard. Prior to her graduate studies, Dr. Joachim earned her BS in Biology with a minor in Chemistry from The College of New Jersey.

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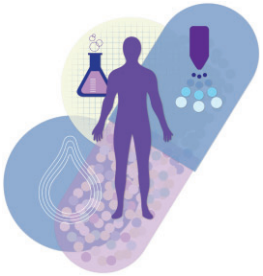
Modified Release Technologies



Catalent, with its broad toolkit of drug formulation and delivery technologies, offers a number of solutions for drug developers looking for modified-release dosage forms. These include the use of enteric coatings on traditional softgels, or the use of its OptiShell® gelatin-free softgel capsule technology, which is ideally suited for the encapsulation of higher melting-point fill formulations. The Zydis® platform offers industry-leading orally disintegrating tablet (ODT) formulation for fast-dissolving dose forms, and through the expanded Zydis Ultra technology, drug loadings can be up to four times higher, broadening the range of drug molecules that are now applicable to ODTs. Catalent is highly experienced in offering solutions to clients for controlled-release dosage forms such as bi-layer tablets, drug-layered spheres, as well as tablets within capsules. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com.**

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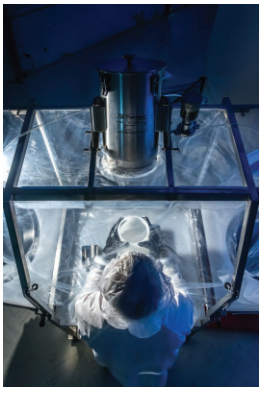

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STANDARD OPERATING PROCEDURES

How Writing an Effective SOP Can Influence Compliance & Build a Better Organization

By: Heidi Stuttz

INTRODUCTION

When it comes to developing internal procedures, drug firms must devote time, diligence, and meticulousness in the development of a safe product design, materials sourcing, manufacturing, and quality control. Per the Food and Drug Administration (FDA) regulations, standard operating procedures (SOPs) are an important part of the primary documentation requirements under good manufacturing practices (GMPs), and they must be in place to successfully navigate an FDA inspection.

It is important to note the FDA has no requirement for what constitutes an SOP or how it should be formatted, yet one of the first items a consultant or FDA auditor will request is a list of SOPs for the system or subject area in question. SOPs are expected to be written clearly, concisely, and easy to follow. They are the driving force behind every activity in your organization. A well written SOP is essential to compliance and business efficiency.

Writing a clear and concise SOP should not be a task taken lightly and its development, when done properly, can be more detailed and complicated than initially imagined. An SOP can provide subjective evidence that your company is organized and has the instructions for your employees to carry out tasks in a consistent, compliant manner.

THE TEMPLATE

Creating a template with a framework of expectations is a simple, yet effective way to drive compliance in your organization. This template should lay the groundwork for expectations across the various departments in your organization. Templates support alignment, provide an opportunity for consistency, and promote an environment in which everyone can follow instructions in a consistent manner.

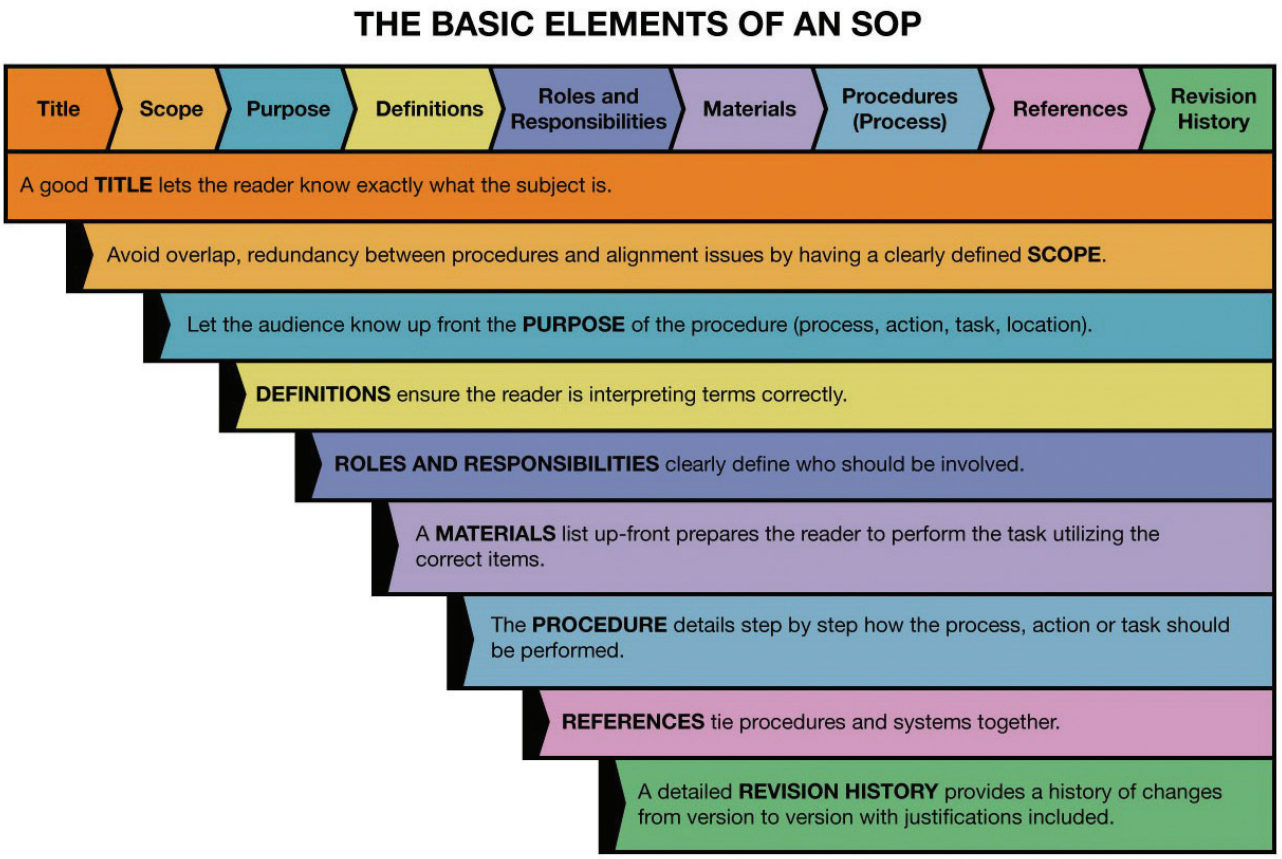
The following summarizes a common outline used in many companies and will explore the essential elements of a well written SOP. This template will be effective whether developing an SOP from scratch or remediating a current system of SOPs and will foster success in every area of your company in which it is implemented.

TEMPLATE ELEMENTS

Title

A title should be simple and accurately describe the intent of the SOP. The document should capture everything the title conveys. For example, "Operation of" should be limited to the operation of an instrument or piece of equipment. This document can expand to include "Operation and Maintenance of" and would include both topics. The title should be short, comprehensive, and limited to the scope of the document.

FIGURE 1



Purpose

Purpose is an opportunity to expand upon the title, explaining to the employee what objective the SOP is intending to achieve. The purpose should be short and typically one sentence. If the purpose covers several topics, this is indicative of the need to consider separating the SOP into additional SOPs.

Scope

The Scope of an SOP discusses the range of activities that the SOP applies to, as well any limits or exceptions not covered by the SOP. A well written scope should have clear parameters and not include any extraneous information. If the system, equipment, or tasks have additional instructions not within the scope, another SOP may be warranted, or the scope can be expanded. In this case, ensure that the title is adjusted to capture additional activity regarding the subject.

Definitions

Internally, companies may have specific definitions, acronyms, or abbreviations that must be spelled out. The interpretation of a term will have a critical impact on compliance. For instance, Water for Injection is much different than Water for Irrigation. While the two are similar, the details in the separate definitions have impact to the expectations. The devil is in the details so to speak. Many companies would benefit from a global glossary of terms to ensure alignment of interpretation across an organization. The global glossary should be built with the definitions and abbreviations that are part of the SOPs, deriving from industry standard definitions that can be tailored for your organization where needed.

Materials

A materials section, though not commonly used in most operational SOPs, can be very important in test methods, laboratory SOPs, and calibration and maintenance procedures in which specific equipment and/or instruments are required in order to perform the tasks. It should simply list the specific equipment, instruments, weights, gauges, etc. that should be used to execute the SOP.

Safety

Essential to the company's safety program, a well written SOP should have a safety section in which PPE (Personal Protective Equipment) is listed. This section of a procedure can also list the prerequisite safety training necessary to perform a task

safely. The document therefore feeds directly into your EHS program for robust safety compliance initiatives.

Procedure

Many companies struggle with this section of the document. This is the heart of a well written, concise, easy to follow SOP. The procedure section should be instructional. Each step should be in sequential order. Anyone with the appropriate prerequisite skills and knowledge should be able to pick up the document and complete the targeted task or operation. The procedure portion should easily translate into a process flow diagram for a visual aid.

Roles & Responsibilities

The roles and responsibilities section of an SOP should include a list of the types of employees that are required to perform some or all the tasks within an SOP. For example, QA inspector, Maintenance Tech, Quality Manager, Manufacturing Operator, etc. Next to each role, a list of the specific activities that are to be performed by each person should be listed. It is common for this section to be in a tabular format. The Roles and Responsibilities section feeds directly into a good organizational chart, job descriptions, skills and competencies required, training, and resourcing. This is a vital element of a well written SOP.

References

The basic rule of thumb for outlining the references in this section of a template is to ensure that all documents required to support a task are acknowledged. This can include other SOPs, forms, government regulations, guidance documents, company policies, etc. To further ensure that documents retain their own scope, pointing to references should also tie documents together within a system. Another rule to follow for listing references is to ensure that all prerequisite tasks leading up to the subject SOP and all subsequent SOPs where necessary are linked to the SOP to demonstrate a comprehensive system and process. For instance, for an operational SOP, if the maintenance SOP is separate, it is appropriate to list this procedure as a reference. Within the document, any references to separate required tasks or awareness related documents should be listed, especially if it is related to the task at hand.

Listing references has a direct impact to change control assessments, investigations and deviations, continuous improvement initiatives, system impact assessments, etc. Whether or not your company is using a document management system, references are key to identifying and evaluating system health and ongoing compliance requirements.

RELATED CONSIDERATIONS

The following areas and tools are directly tied to SOPs and have a major role in organizational compliance initiatives.

Documentation

Simply instructing someone to perform a task is of no consequence if a document is not available to record the proof that the task was performed. Many companies are apprehensive about the use of forms that must be controlled and audited for GDP and GMP compliance. The only evidence a task has been performed correctly is a document that offers proof of that completion.

Whether your SOP describes the requirements to use a log book, calculation sheet, or performance of a test, the associated addendum or form must be present to allow the required documentation. The only way that paper documentation would not be required is the use of a validated computer system to capture the activity.

Metrics

Assessing compliance to any procedure requires measurable metrics. Measurable metrics are the backbone of illustrating adherence to procedural compliance. This can include, completing forms, entering data into a computer system, performing audits, etc. When writing an SOP, creating measureable metrics should always be considered whether you are using those metrics for proper resourcing, schedule adherence, continuous improvement opportunities, or standard quality management monitoring.

Process Flow Diagrams

Each SOP, whether a stand-alone document or part of a system or operation may benefit by being depicted in a process flow diagram. This can ensure that steps are sequential, there are no gaps in the procedure, that the procedure fits into the system appropriately, and that the roles and responsibilities make sense in the document. Process Flow diagrams make great training tools, as most people benefit from visual aids. It also assists your organization when considering changes.

Streamlining, Obsoleting, New

Regardless if your company is new or

you are requiring/experiencing a remediation, the question about the number of documents is very common. If you believe there are too many documents or that documents are hard to follow due to scope creep or complexity, sometimes streamlining should be considered in the overall document architecture. There is no right or wrong way to structure your database of procedures. What is required is that they are easy to follow, are executed properly, and are managed within a structured document control system.

Technical documents that are complex in nature are better when they are broken down into isolated tasks and tied together sequentially. Agencies and auditors will question the competency and compliance of a process if a document is too long (ie, 50+ pages) and the person(s) responsible are only required to "read and understand."

An SOP structure should be well thought out up front, as the strategy of training is directly impacted. Once an SOP or group of SOPs become effective, it can require extensive effort to change the document as it evolves. Training is also directly impacted and should always be evaluated as changes occur in SOPs.

On that note, it is important to plan for how revisions to the SOP will be handled and titled. Revision control is crucial for SOPs (and all other types of controlled documents) to ensure that all changes are tracked and monitored (change control), referenced procedures are evaluated for changes, necessary checklists are attached, and other documents are updated in accordance with the revision — and to ensure only current versions of the procedures are in use. Revisions must include traceability for previous processes and product manufacture. Ultimately, the quality unit reviews and approves all changes for compliance with cGMP regulations and other statutory requirements.

Another strong consideration when developing, changing, or improving a process or system, is the training strategy. If operation and maintenance of a system is separate, this can have an impact on who is required to be trained. If your maintenance personnel are required to have operational knowledge of a system to perform maintenance, they may be required to train on both the operation and maintenance if the SOPs are separate, or have training targeted to a portion of the SOP that is different from an operator if they are together.

Resourcing & Planning

Proper resourcing is imperative for a company to ensure they can attain and maintain compliance to their processes and systems.

CONCLUSION

SOPs are more than just documents in a database or file room. They are a key factor in your company's success or failure. Key elements of a template drive alignment within your company organizational structure and corporate architecture. The ability to attain and maintain compliance is essential to success, as failures usually involve document revision.

Use of an SOP template that ties into your company's systems and structure will certainly support successful compliance. It eliminates shortcuts, ensures that all systems are congruent, and builds efficiency and optimization. In turn, it can avoid costly remediation when well strategized. The ability to eliminate gaps, resource properly, identify qualified materials, properly outline job descriptions, and develop your organizational chart are many of the benefits of a well written SOP. Writing an effective SOP can influence compliance and build a better organization. ◆

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BIOGRAPHY

Heidi Stuttz is EAS Consulting Group's Independent Consultant and is an expert in biotech and medical device oversight. She assists clients with a variety of projects, including R&D programs, FDA submissions, EMEA dossiers, compliance enhancements, and quality improvement initiatives. Assisting with product development processes from clinical trials to commercialization, she demonstrates proven success with facilitating product development and moving regulatory programs forward. She is experienced with Auditing cGMPs for Continuous Process Improvements, FDA ISO9000 Qualifications, Developing and Managing QMS Implementation Strategies, Records Management, Laboratory Compliance/Controls, Validation and Remediations of Equipment, Process, Facilities and Utilities, and has driven Operational Readiness and Inspection Readiness. EAS Consulting Group is a leading FDA regulatory consulting firm working in all FDA regulated industries. For more information, visit www.easconsultinggroup.com.

CLINICAL STUDY REPORTING

Assessing the Value of Interim Analyses in Clinical Trials

By: Paul Stark, MS, ScD

INTRODUCTION

Phase 3 trials are the most extensive and rigorous types of scientific investigations of a new intervention, with the objective to compare the efficacy and safety of the new intervention to the standard-of-care. In these randomized trials, the sample size needs to be sufficiently large in order to make the proper assessments.

Data needed for sample size calculations usually comes from studies on similar drugs, devices or compounds, small-scale studies, and historical data. With these estimates coming from vastly different sources, estimates are apt to be imprecise. Thus, interim analyses provide an opportunity to update these values during the study or uncover issues that necessitate stopping the study early.

This following will review how and when an interim analysis would be valuable and how, with examples and outcomes, it can be applied in a clinical trial setting.

WHAT IS AN INTERIM ANALYSIS AND WHY IS IT IMPORTANT?

An interim analysis compares randomized arms at any time point before the end of a Phase 3 trial and usually occurs before recruitment is complete. It is especially appealing to the regulatory agencies and the sponsor, allowing for decisions and changes to be made in the middle of the study. The analysis provides several options and opportunities for the trial, for example:

- An opportunity to re-estimate the sample size
- An opportunity to modify the trial design
- An option to stop the trial for efficacy or futility
- An option to continue the trial as originally planned.

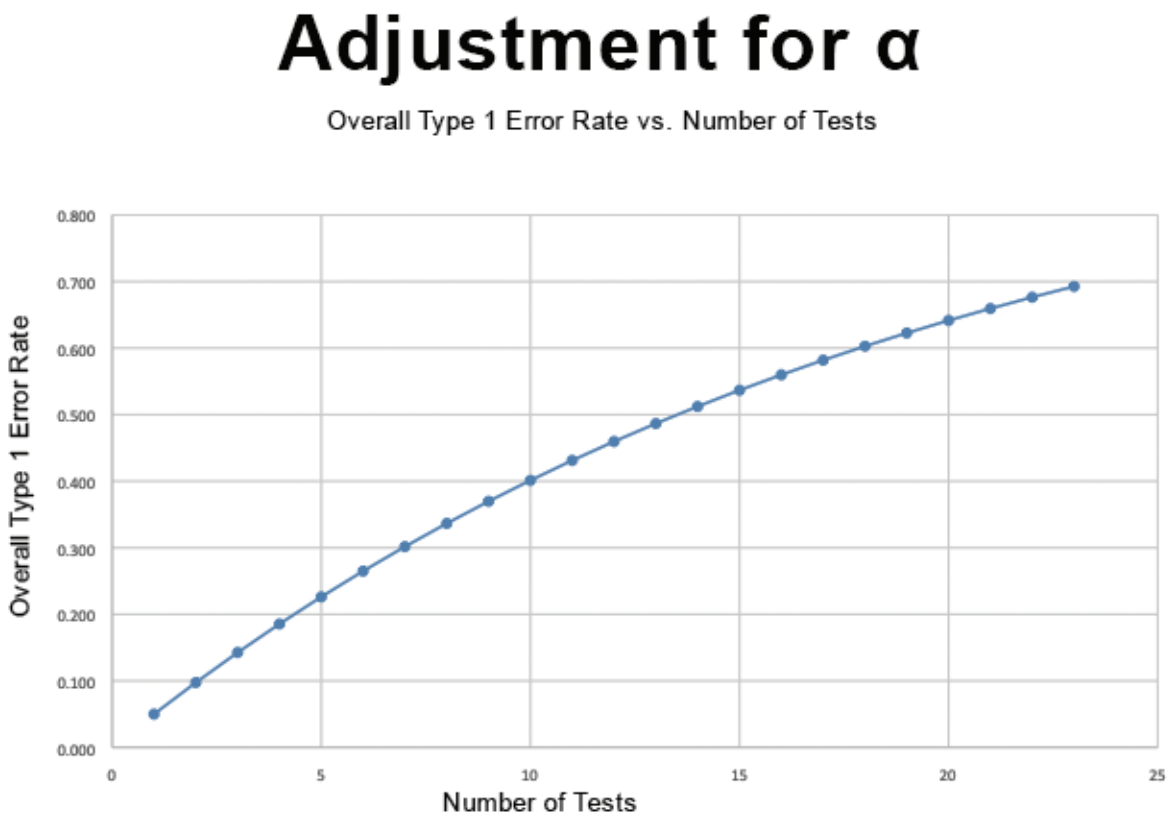
As Phase 3 trials are generally cost-intensive, it makes sense to insert an interim analysis in the planning protocols of the trial, particularly as a Phase 3 trial is needed to gain FDA or EMA approval.

Depending on the disease prevalence and the required number of subjects for the study, a traditional Phase 3 may take a couple of years to recruit and a couple of years to follow the patients. By the time the last subject enters the study and has his or her last visit, it could be years between the first patient in and the end of the study. It's a long time to go without any real knowledge about the efficacy or safety of an intervention.

WHEN TO CONDUCT AN INTERIM ANALYSIS

The timing, frequency, and methods for the analysis should always be specified in the trial protocol before the study starts. There may be a single analysis or more at different points of time depending on the number of subjects and the drug or device being tested. The analysis needs to be timed when there are enough subjects enrolled in the trial to "see something" (ie, the less data you have, the harder it is to see signals). On the other hand, you don't want to conduct an analysis so far into the study that there's little value. For example, If 90% of the subjects have already been enrolled and you do an interim analysis and find you should drop one treatment arm or stop the study early, the benefits of the interim analysis, in terms of cost savings or the safety of the subjects, are limited. Generally, depending on the size and scope of the trial, midway through is a good point to conduct the analysis. Additionally, there may need to be an adjustment of alpha to preserve the overall Type I error rate of the study.

FIGURE 1



Adjustment of alpha may need to occur to preserve the overall Type I error rate of the study.

STATISTICAL APPROACHES WITH THE INTERIM ANALYSIS

When a study is conducted, it is necessary to determine the number of people that need to be enrolled to show a statistically significant treatment benefit, if one actually exists. So, the method for doing a sample size calculation means there needs to be previous knowledge of treatment responses and how impactful the treatment is expected to be.

These values are typically found in previous Phase 2 studies or literature from a comparable drug in the same family. But those estimates are not always accurate. Sometimes a study will be conducted thinking there might be, for instance, a 10-point benefit in cholesterol reduction; however, there was only a 7-point benefit. But even though the 7-point benefit might be clinically relevant, because the study wasn't large enough, it isn't statistically significant and therefore the drug wouldn't pass regulatory approvals.

One way to use the interim analysis is to re-estimate the sample size to make sure the assumptions made in the sample size estimate are holding. Another is to stop the study because it's doing so well the results will be statistically significant or stop the study because it's doing poorly. There might be a modification in the study design, ie, if there are three arms in the study with a low dose of the drug or high dose of the drug or standard of care, the analysis might show that the effect is only pronounced in the high-dose group, but not the low-dose group. Therefore, enrollment would stop in the low-dose group. Or it might show that everything is going as planned and the study would continue as is.

When a statistical analysis is conducted, a p-value is calculated, which is the probability that results seen are due to chance alone. If, for example, the p-value is 0.04, that means 4% of the time there would be as big of a difference observed in the two treatment arms just by chance alone, even if both arms were the same. And so that would result in rejecting the null hypothesis of no difference between the arms.

That is known as a false positive, incorrectly rejecting the null hypothesis and concluding a difference in treatments, which is also called a Type I error. Every time the data are analyzed, there's a 5% chance of making a Type I error, if alpha=0.05. As the number of analyses increase, the chance of making a Type I error also increases. As a result, an alpha adjustment is often required.

APPROACHES FOR ALPHA ADJUSTMENT

An alpha adjustment is needed to preserve the overall Type I error rate. Not surprisingly, researchers have established different methods to account for multiple analyses and ways to adjust the alpha. There isn't any one consensus but there are a few that are commonly used.

- Pocock
  - Same alpha for interim and final analysis
  - 2 analyses, a = 0.0294
- Haybittle-Peto
  - Very strict alpha adjustment at interim, no adjustment at final
  - 2 analyses, a = 0.002 at interim and a = 0.05 at final
- O'Brien-Fleming
  - Strict alpha adjustment at interim, small adjustment at final
  - 2 analyses, a = 0.0054 at interim and a = 0.0492 at final

OUTCOMES OF DIFFERENT METHODOLOGIES - EXAMPLES

The application of different methodologies can make a significant difference in the outcome of a study as outlined by the following contrived example (although similar situations have been experienced in real-life studies). Let's say we are designing a pivotal Phase 3 clinical trial to compare a new treatment to standard-of-care. The outcome is "treatment success." Based on the results of an earlier Phase 2 study, the expected percent of treatment success is 34% in the experimental group and 20% in the control group. The sample size calculation yields that 414 subjects are needed (207 in each arm) to achieve 90% power at alpha=0.05. Once the study is conducted, the results are as follows:

Treatment Arm

- 59 successes at end of study (28.5%)
- 30/104 (28.8%) at interim

Control Arm

- 41 successes at the end of the study (19.8%)
- 20/104 (19.2%) at interim

Scenario No. 1 - No Interim Analysis

	Treatment	Control
Success	59	41
Failure	148	166
Total	207	207
End of study p-value = 0.041 – Reject null hypothesis of no difference in treatments.		

Scenario No. 2 - 1 Interim Analysis - Midway

	Treatment	Control
Success	30	20
Failure	74	84
Total	104	104
Interim p-value = 0.1442 – fail to reject null hypothesis		

WHAT'S THE CONCLUSION

At the end of the study, the p-value was 0.041, which was less than 0.05, so without an interim analysis, the results would suggest a statistically significant treatment difference. However, conducting the interim analysis necessitated an adjustment of the alpha at the end of the study and depending on which method was chosen, there were different conclusion. If Pocock was used, the null hypothesis would not have been rejected. However, if O'Brien-Fleming was used, the null hypothesis would have been rejected. Clearly the methodology chosen had an important impact on this study example.

How to decide which methodology to use is not an easy choice for pharma or medical device companies. Different methods have different assumptions and scenarios. If, for example, a new drug is viewed as extremely promising, and the study has the potential to meet the strict alpha threshold at the interim analysis, O'Brien-Fleming might be favored over Pocock, in the hopes of stopping the study for benefit at the interim analysis, saving time and money.

IS AN INTERIM ANALYSIS ALWAYS BENEFICIAL?

With the time and investment involved in clinical trials, particularly if the drug or device has advanced to the Phase 3 level, it's incumbent on all involved, from the sponsor as well as partners like the CRO, to carefully decide whether an interim analysis is appropriate in the specific setting. If so, all details about the timing, frequency, and method should be specified in the trial protocol before the study starts.◆

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BIOGRAPHY

Dr. Paul C. Stark is the Director of Biostatistics for PHASTAR, Inc. and the head of the Cambridge, MA, office. He has more than 20 years of experience designing and analyzing data from clinical trials, surveys, observational studies, and large datasets. Dr. Stark earned his undergraduate degree from Cornell University and his MS and Doctoral degrees from Harvard University. He has served as the Director of Biodata Sciences at Clinlogix and the Director of Biostatistics and Epidemiology at New England Research Institutes. Before working at NERI, he was a Professor and the Director of Statistics at Tufts University for almost a decade and is still an Adjunct Professor.He has authored or co-authored more than 70 articles in peer-reviewed journals, focusing on statistics, cardiology, nephrology, oral-health research, and oncology.

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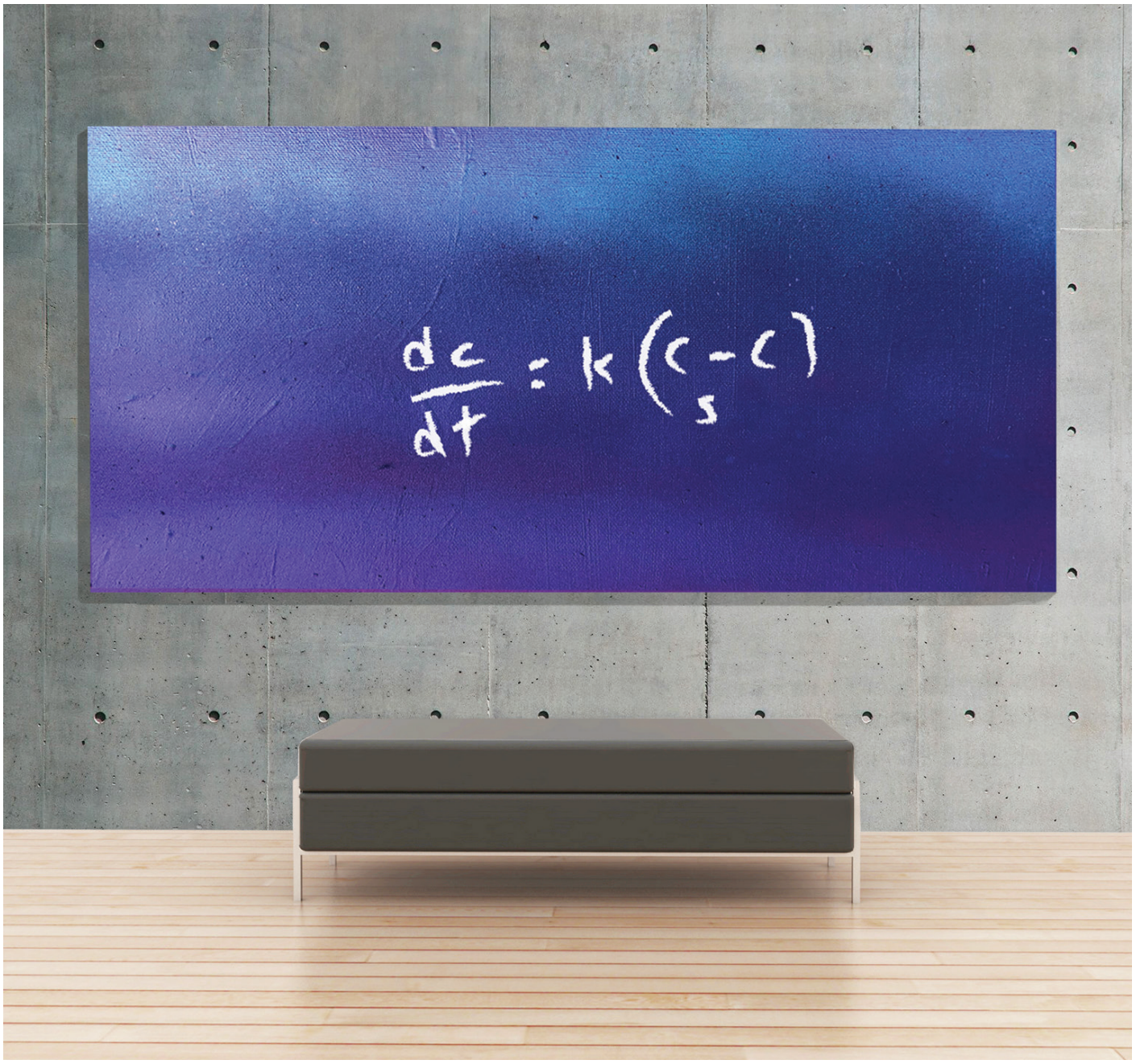

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