Drug Development® & Delivery

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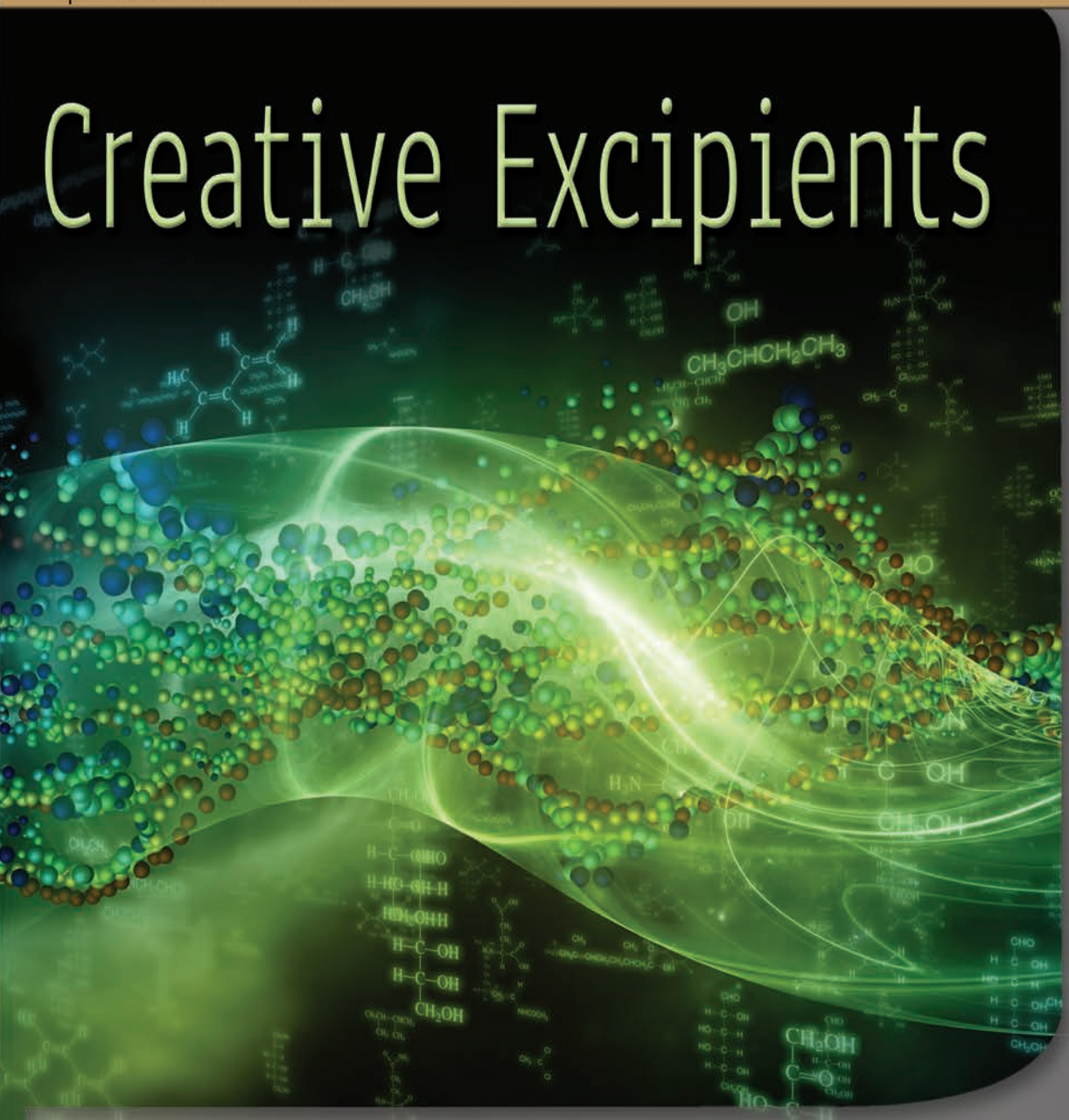
Creative Excipients



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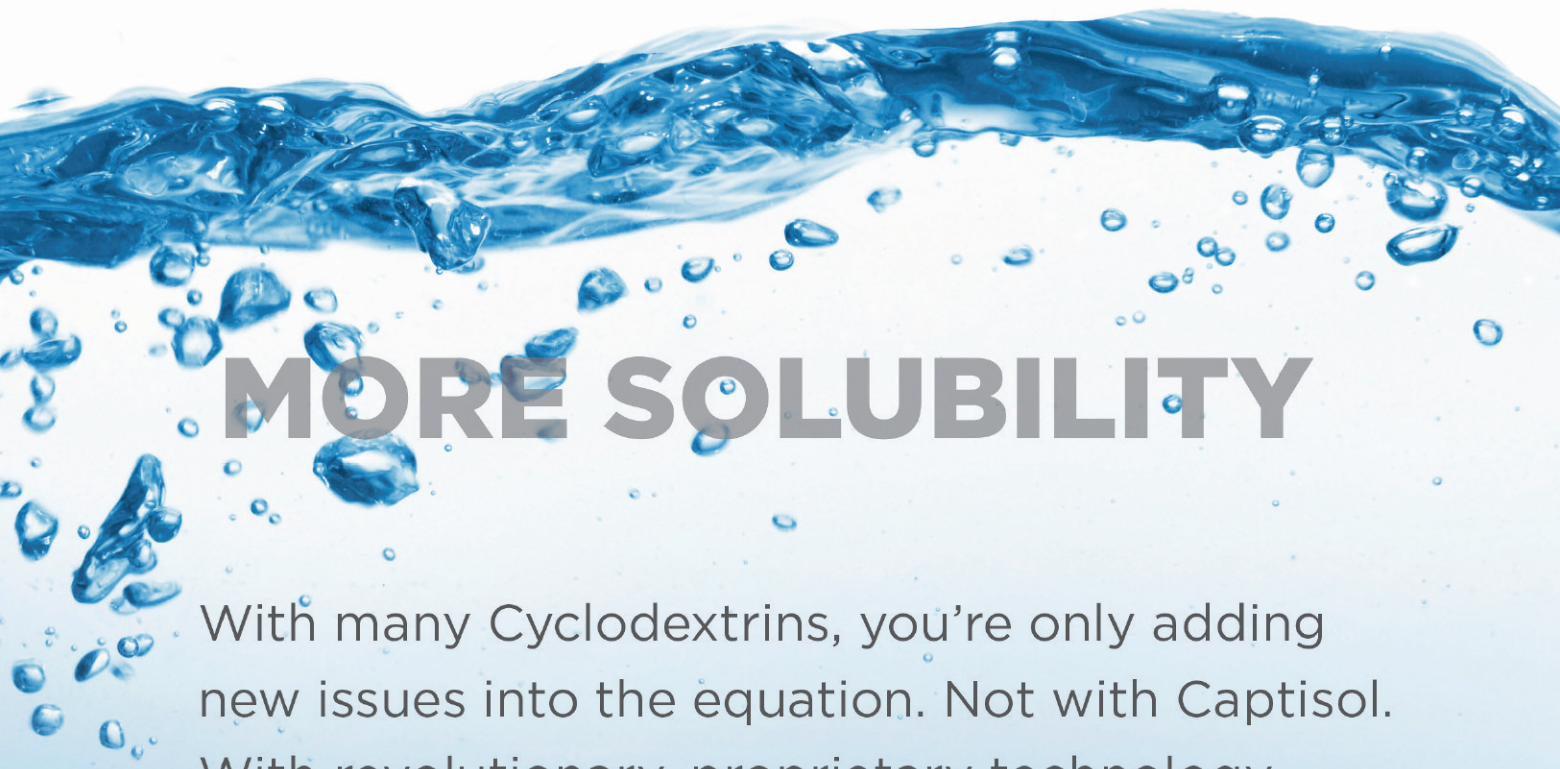

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Prefilled Syringes

"The shape of prefilled syringes and the small volumes they contain make them challenging to inspect for particles and cosmetic defects. Automated inspection systems greatly reduce the time needed for inspection and improve the detection of defects."

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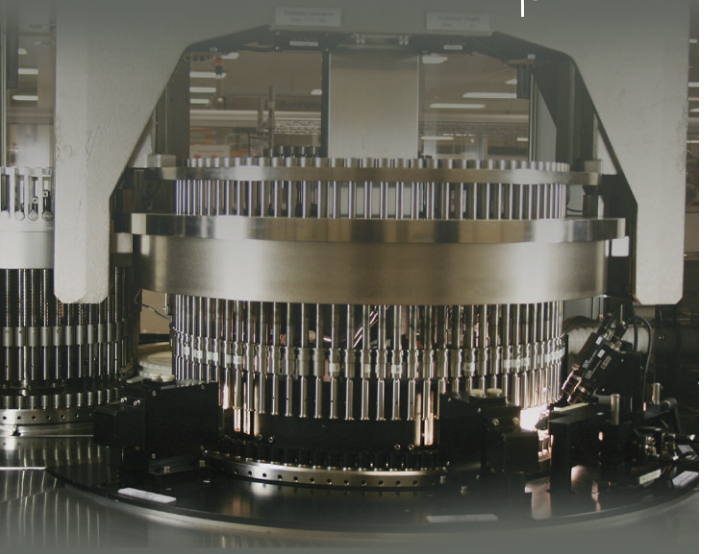

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"As the interest in polymers/excipients and the formulation technologies continue to rise, so does the interest in new and innovative excipients/solubilizers for achieving the desired solubility and bioavailability. Thus, the industry is taking aim at finding excipients with excellent solubilizing properties."

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- DEBATE: Pearls of Wisdom, Nano-delivery to Solid Tumors: Is there hope?
- and more

Review the full program and register at **2018.controlledreleasesociety.org**

#CRSnyc

CicloMed Announces First Patient Dosed With Ciclopirox Prodrug in Phase I Trial

CicloMed LLC recently announced that the first patient has been dosed in a Phase I clinical trial. The CPX-POM-001 study is characterizing the safety, dose tolerance, pharmacokinetics and pharmacodynamics of Ciclopirox Prodrug, or CPX-POM, in patients with advanced solid tumors.

Under the leadership of the study's Principal Investigator, Howard A. "Skip" Burris III, MD, Chief Medical Officer and President, Sarah Cannon Research Institute, the first-in-human trial will enroll patients at several US sites. This initial clinical trial aims to determine the recommended intravenous dose of CPX-POM for subsequent Phase II trials.

"Ciclopirox Prodrug has demonstrated anti-tumor activity in preclinical models of non-muscle invasive and muscle-invasive bladder cancer. There is preclinical evidence for activity in both forms of the disease, particularly in inhibiting the progression from non-muscle invasive to muscle-invasive bladder cancer. This trial represents an important first step in our strategy to evaluate the combined activity of Ciclopirox Prodrug and standard-of-care surgical, chemotherapy and immunotherapy treatments in bladder cancer patients," said Tammy Ham, President and Chief Executive Officer of CicloMed LLC.

CPX-POM was discovered by researchers at The University of Kansas Cancer Center and KU's Institute for Advancing Medical Innovation (IAMI). CicloMed was formed in 2016 as a unique public-private partnership between BioNovus Innovations LLC and IAMI. Development of CPX-POM for the treatment of bladder cancer is the lead development program under this partnership. "Our vision is to discover and advance to patients promising new cancer treatments. This achievement represents a major milestone for our program," commented Roy Jensen, MD, Director of the University of Kansas Cancer Center. For further information, please view the Phase I study's disclosure page or search for CicloMed or CPX-POM on www.clinicaltrials.gov.

More than 500,000 men and women are living with bladder cancer in the US. Bladder cancer is the fifth most common cancer in Americans and the fourth most common cancer in men. According to the American Cancer Society, about 79,000 new cases of bladder cancer will be diagnosed this year, and 16,800 deaths are expected due to the disease. Of all known malignancies, bladder cancer has the highest recurrence rate, and bladder cancer also has the highest lifetime treatment costs per patient of all cancers.

CicloMed is a developmental-stage pharmaceutical company focusing on unmet medical needs in oncology, and Ciclopirox Prodrug is its lead drug candidate. CicloMed is a subsidiary of BioNOVUS Innovations LLC, a Kansas City-based firm committed to investing in individuals and organizations who are transforming healthcare and bringing novel solutions to reality. Portfolio companies have developed new enabling technologies, pharmaceuticals and delivery models that are transformative. For more information, visit www.ciclomed.com.

Enteris BioPharma Initiates Feasibility Program With Ferring Pharmaceuticals to Develop Oral Formulation of a Peptide

Enteris BioPharma, Inc. recently announced it has entered into a feasibility development agreement with Ferring Pharmaceuticals to utilize Enteris' proprietary oral delivery platform, Peptelligence, to develop an oral formulation of a peptide-based injectable therapeutic from Ferring.

Under the terms of the agreement, Enteris will conduct feasibility studies to develop an oral formulation of an undisclosed peptide therapeutic from Ferring. Based on the results of the feasibility program, Ferring will have the option to license the oral tablet formulation from Enteris. This new agreement between Enteris and Ferring adds to several ongoing projects between the two companies, including a licensing agreement announced in January 2017.

Joel Tune, Chief Executive Officer and Executive Chairman of Enteris BioPharma, remarked "We are very pleased to extend our relationship with Ferring and explore the potential of Peptelligence to successfully enable the oral delivery of this peptide therapeutic. For Enteris, this latest agreement comes at time of significant growth as we continue to advance our internal pipeline, led by Ovarest, and target additional opportunities to leverage the power of Peptelligence to enable the oral delivery of peptide-based medications that must otherwise be administered by injection."

Ferring Pharmaceuticals is a research-driven, specialty biopharmaceutical group committed to helping people around the world build families and live better lives. Headquartered in Saint-Prex, Switzerland, Ferring is a leader in reproductive medicine and women's health, and in specialty areas within gastroenterology and urology. Ferring has been developing treatments for mothers and babies for over 50 years. Today, over one third of the company's research and development investment goes towards finding innovative and personalised healthcare solutions to help mothers and babies, from conception to birth. Founded in 1950, Ferring now employs approximately 6,500 people worldwide, has its own operating subsidiaries in nearly 60 countries and markets its products in 110 countries.. To learn more about Ferring or its products please visit www.ferring.com.

Enteris BioPharma, Inc. is a privately held, NJ-based biotechnology company offering innovative formulation solutions built around its proprietary drug delivery technologies. The company's proprietary oral delivery technology – Peptelligence – has been the subject of numerous feasibility studies and active development programs, several of which are in late stage clinical development. Additionally, Enteris BioPharma is advancing an internal product pipeline of oral tablet reformulations of drug products that address significant treatment opportunities for which there is no oral delivery option. Enteris BioPharma's most advanced internal product candidate, Ovarest® (oral leuprolide tablet), is an oral peptide being developed for the treatment of endometriosis. Tobrate® (oral tobramycin tablet) is also being developed by Enteris BioPharma for the treatment of uncomplicated urinary tract infection (uUTI). A third internal compound, octreotide, will be entering preclinical development in 2018.

Ginolis Provides Mobidiag High Throughput Manufacturing Lines for Growing Needs of Novodiag Cartridges

Ginolis Ltd recently announced it has signed an agreement with Mobidiag Ltd, a Finnish molecular diagnostics for infectious diseases company. Through the implementation of cutting-edge production lines from Ginolis, Mobidiag will be able to answer growing needs in molecular diagnostics for routine use and anticipate the production of upcoming Novodiag test cartridges.

Launched in December 2017, the new Novodiag solution allows direct analysis of a patient sample placed in a disposable cartridge and delivers comprehensive results in about an hour, compared to days with well-established culture methods. Novodiag helps make treatment decisions faster and more accurate, avoiding for example the unnecessary use of antibiotics.

"The innovative Novodiag cartridge has been developed at Mobidiag thanks to the combination of multidisciplinary teams and expertise. The cartridge includes state-of-the-art technologies, such as qPCR and microarray, bringing with them some specific requirements and constraints. We then needed to successfully automate our processes and move from a small-scale production capacity to industrial volumes without compromising quality and costs. Thanks to its cutting-edge modular platforms and expertise in diagnostics processes, we are confident that Ginolis will bring the most relevant solution to support us in our growing activity", says Tuomas Tenkanen, CEO at Mobidiag.

The manufacturing solution developed for Mobidiag is based on Ginolis' modular Xanthia automation platform. Its compact and modular design allows for high quality automation within a small footprint, saving valuable space in the clean room environment. In addition to Ginolis' patented dispensing technology, the line is equipped with laser welding, precision assembly, ultrasonic welding and line confocal imaging (LCI) for quality inspection.

Antibiotic resistance is one of the greatest threats to the world's health. According to the World Health Organization, the number of antibiotic-resistant bacteria grows at an alarming rate worldwide and all efforts should be taken to stop this development. Fast and reliable diagnostics are needed to detect resistance and thereby reduce the use of antibiotics.

With rapid tests and high-capacity production lines, Mobidiag is able to respond to rapidly growing requirements for infection diagnosis, including antibiotic resistance. A Novodiag cartridge currently under development and planned to be released in mid-2018.

The Novodiag solution allows direct analysis of a patient sample placed in a disposable cartridge and delivers comprehensive results in about an hour. Combining qPCR and microarray technologies, Novodiag offers an all in one solution for on-demand targeted and syndromic testing.

This molecular diagnostic solution offers an easy to use and cost-efficient method, with very limited hands-on-time and without the need for much technical expertise. Novodiag is particularly suitable for low volumes and on demand testing for clinical laboratories. Learn more about Novodiag.

Dalton Announces a Drug Development & GMP Manufacturing Services Agreement With Oryn Therapeutics

Dalton Pharma Services has recently announced the signing of a drug development and manufacturing services agreement with Oryn Therapeutics, an American biotechnology firm committed to the clinical development of novel and affordable drugs to address unmet medical needs in autoimmunity, inflammation and infectious diseases.

Under the signed agreement, Dalton will provide drug development and cGMP aseptic liquid filling of ORTD-1 in glass vials which will be used for Phase-1 clinical studies of ORTD-1 by the 3rd quarter of this year.

ORTD-1 is a first-in-class drug for treatment of rheumatoid arthritis (RA). RA affects about 1% of the population worldwide. It is the third most common type of arthritis and causes more disability than any other condition, including heart disease, diabetes, and back/spine problems. Due to its severely debilitating nature in advanced stages, it accounts for 22% of all deaths from arthritis and other rheumatic conditions. ORTD-1 treatment of experimental arthritis in rats has been shown to induce remission of established disease after only 9 days of treatment. The remission is long lasting (2 to 3 months) after treatment is discontinued.

"Dalton is privileged to be associated with Oryn in its commitment to develop a safe and effective first-in-class drug treatment for RA", said Peter Pekos, CEO and President, Dalton Pharma Services.

Oryn is a biopharmaceutical company leveraging its proprietary knowledge and paradigm changing approach to drug development utilizing the structural and biologic properties of theta defensins, cyclic peptides that evolved over billions of years to develop novel therapies to address the unmet medical needs in autoimmunity, inflammation and infectious diseases. They are the industry leaders in R&D of theta defensins and development of methods for synthetic and recombinant production of macrocyclic Orynotides, peptide derivatives of macrocyclic theta defensins that are stable, non-toxic, non-immunogenic and non-immunosuppressive. Oryn has developed and patented a technology that gives it a technical edge in the design, functional analysis, and production of Orynotides. These efforts have uniquely positioned Oryn to develop new classes of clinically valuable therapeutics. For more information, visit http://www.oryntherapeutics.com.

Dalton Chemical Laboratories Inc. o/a Dalton Pharma Services is a Health Canada-approved and FDA-registered cGMP contract service provider of integrated chemistry, drug development, and manufacturing services to the pharmaceutical and biotechnology industries. We bring 30 years of experience to our client's projects and emphasize quality, speed and flexibility. Dalton can accelerate your drug development program by integrating process development, cGMP API manufacturing, cGMP sterile fill/finish, and solid finished dose manufacturing, all at a single location. For more information, visit https://www.dalton.com.

Gerresheimer Unveils Innovative Vials Made From Glass & Plastic

Gerresheimer's booth at the PDA Annual Meeting – held at the Loews Sapphire Falls Resort in Orlando from March 19 to 21 – was to focus on innovative glass and plastic vials for parenteral drugs that place high demands on the barrier properties and, by extension, the safety of their primary packaging.

Gerresheimer has invested many years in developing and producing its plastic MultiShell vials and glass Gx Elite vials in order to offer its customers primary packaging solutions that are ideal for sensitive active substances.

"It is absolutely crucial for drugs to be packaged properly in order to ensure drug stability," says Edward Troy, Vice President Sales & Marketing and product expert for glass. "The question of whether to use glass or plastic vials depends on the application. We aim to work with our customers to find the best possible solution for their parenteral drugs."

Gx Elite vials' quality and performance is a result of proprietary techniques employed in the manufacturing process. As a result of these proprietary techniques, the Gx Elite vials have a significant improvement in glass strength and reduced cosmetic defects. A vial that resists delamination protecting the valuable drug product.

The transparent, shatter-resistant MultiShell vial has an innovative multilayer structure made from COP and PA.

"The kind of powerful active ingredients that are being developed nowadays need shatter-resistant packaging and improved barrier protection," says Franck Langet, explaining the properties of the Gx MultiShell vial. With its innovative multilayer structure made from COP and PA, this transparent vial is a unique packaging solution that meets all these requirements. Gerresheimer offers vials holding 2, 5, 10, 15, 50, and 100 ml, which are also available as ready-to-use versions including validated gamma sterilization. Gerresheimer supplies both COP multilayer and monolayer containers.

Gerresheimer operates with the world's latest technologies and monitoring processes from the development stage right through to production and packing for delivery. Gerresheimer uses cutting-edge clean room technology to guarantee optimum cleanliness for its products in terms of particles and germs. With bases in Europe, Asia, and the Americas, Gerresheimer specializes in manufacturing primary packaging for pharmaceuticals in line with the relevant pharmacopeias. All its factories are currently certified to standards including ISO 9001.

Gx and MultiShell are registered trademarks of the Gerresheimer Group.

Gerresheimer is a leading global partner to the pharma and healthcare industry. With specialty glass and plastic products, the Company contributes to health and well-being. Gerresheimer operates worldwide and its approximately 10,000 employees manufacture products in local markets, close to its customers. The comprehensive product portfolio includes pharmaceutical packaging and products for the safe, simple administration of medicines: Insulin pens, inhalers, prefillable syringes, injection vials, ampoules, bottles, and containers for liquid and solid medicines with closure and safety systems as well as packaging for the cosmetics industry.

Cesca Therapeutics Expands CAR-TXpress Intellectual Property Portfolio

Cesca Therapeutics Inc. recently announced its device subsidiary, ThermoGenesis Corp., has filed a patent with the US PTO for a method of further simplifying the processes of T-cell activation and transduction within the company's proprietary CAR-TXpress workflow.

"As we pursue our goal of providing an automated means of manufacturing new immunotherapies such as CAR-T, it is critical that our innovations are recognized by the USPTO and other global intellectual property regulatory agencies," said Dr. Chris Xu, Chief Executive Officer of Cesca. "We believe this new patent application, if and when granted, will significantly improve the commercial appeal of our CAR-TXpress technology by further extending the number of manufacturing steps that may be performed in a "one-pot" process (employing, for example, the cartridge covered by US Patent No. 9,695,394), from initial pre-processing of blood or leukapheresis product through to T-cell activation and transduction. The practice of this latest invention allows purification and activation of T-cells to be completed simultaneously, thus further simplifying the CAR-TXpress workflow and offering the potential for improved efficiency and reduced manufacturing cost, which are the two most significant challenges facing CAR-T developers today."

ThermoGenesis' proprietary buoyancy activated cell sorting (BACS) technology, which is key to the CAR-TXpress platform, is supported by two recently issued US Patents: No. 9,695,394 and No. 9,821,111. BACS technology allows the company to address the needs of a broad range of potential partners by increasing efficiency while lowering the cost to manufacture CAR-T immunotherapy drugs.

BACS technology employs microscopic bubbles to isolate a specific cell type from a complex mixture of cells, such as blood. These microbubbles bear antibodies on their surface, enabling them to bind specifically to a single desired target cell type. When coated with microbubbles, the target cells float to the top of the host liquid, while non-target cells sink to the bottom - a process that can be accelerated by centrifugation. Subsequent collection of the floating target cell layer and release of the cells from their microbubbles provides a highly purified preparation of just the cells of interest, with high recovery efficiency while retaining cell viability.

Cesca Therapeutics develops, commercializes, and markets a range of automated technologies for CAR-T and other cell-based therapies. Its device division, ThermoGenesis, provides a full suite of solutions for automated clinical biobanking, point-of-care applications, and automation for immuno-oncology. The company is developing an automated, functionally-closed CAR-TXpress platform that addresses the critical unmet need for better cellular manufacturing and controls (CMC) for the emerging CAR-T immunotherapy market. Cesca is an affiliated company of China-based Boyalife Group.

US PTO Awards BioPharmX Patent Protection for Novel Tetracycline-Class Topical Drug Compositions

BioPharmX Corporation recently announced the US PTO has granted the first in what the company expects will be a new family of patents protecting its novel topical gel delivery system that allows for greater bioavailability of an active pharmaceutical ingredient (API).

The patent (US Patent No. 9,918,998), titled Pharmaceutical Tetracycline Composition for Dermatological Use, covers a topical composition comprised of minocycline or another tetracycline-class drug and a method for making such compositions. The patent also covers treatments of dermatological inflammation or infection using a minocycline composition. Current formulations protected by the patent include BPX-01 for the treatment of acne and BPX-04 for the treatment of rosacea.

This is the fourth US patent issuance BioPharmX has received. Three earlier-issued US patents protect the company's encapsulation delivery system, which can isolate the API. The most recent of these patents, US Patent No. 9,901,586, titled Dosage Form Comprising an Active Ingredient and a Plurality of Solid Porous Microcarriers, was granted Feb. 27, 2018.

The US No. 9,918,998 patent protects tetracycline-class products carried by BioPharmX's innovative delivery system, which for the first time stabilizes and fully solubilizes these drugs to make them effective in a topical formulation. This includes products that use other tetracycline-class drugs as well as combination products that combine antibiotics with other drugs, for example retinoids.

Oral minocycline has been widely used since the 1970s; however, oral antibiotics tend to flood the body with medicine and are commonly associated with adverse effects that range from nausea to diarrhea. Also, there is growing concern over the rise in antibiotic-resistant bacteria.

In response, the pharmaceutical industry has spent years unsuccessfully trying to develop a stable, soluble topical formulation of minocycline, which produces less resistance than other tetracycline-class antibiotics. BioPharmX is the first company to develop a topical gel formulation of minocycline that reaches targeted areas of the skin, where acne and other conditions develop. By applying minocycline topically, a patient may reduce the systemic uptake of minocycline and focus the drug's beneficial effects at the skin where they are most needed.

BioPharmX has successfully completed a Phase 2b trial for BPX-01 for acne and is in Phase 3 readiness. The company has reported positive interim results from a feasibility study for BPX-04 for rosacea and is preparing for a Phase 2 trial.

In addition to the four patents it has been awarded on two drug delivery systems, the company has more than a dozen patents pending and in process.

BPX-01 and BPX-04 are hydrophilic (non-oil-based) topical gels with fully solubilized minocycline that have been shown to penetrate the skin to deliver the antibiotic to its target. Following positive results from its previously announced Phase 2b dose-ranging study of BPX-01 in acne, BioPharmX continues with Phase 3 clinical study plans for BPX-01 for the treatment of inflammatory lesions of acne.

BioDuro Collaboration With Pfizer Leads to Creation of a Shelf-Stable Fluorosulfation Reagent

BioDuro LLC recently announced the creation of AISF ([4-(Acetylamino)phenyl]-ImidodiSulfuryl diFluoride), a convenient, shelf-stable, crystalline reagent for the synthesis of fluorosulfates and sulfamoyl fluorides. AISF was developed through a research collaboration with Pfizer Inc.

While fluorosulfates have immense potential applications, from chemical biology to polymer chemistry, the currently utilized method of synthesis relies on the use of sulfuryl fluoride gas. Because sulfuryl fluoride gas is a colorless, odorless, and toxic gas that requires specialized equipment and additional safety precautions when using, this potentially valuable functional group has previously not been fully evaluated or broadly adopted.

"This breakthrough is just one example of what deeply committed and engaged scientists can achieve in a collaborative environment," said Cyrus K. Mirsaidi, President and CEO, BioDuro. "The creation of AISF and its development into a commercially viable, and environmentally safe product, is a result of a collaboration between the Pfizer and BioDuro chemistry teams, and one that I look forward to continuing as we seek to address new challenges."

Three key attributes were sought for a solid reagent that could be an alternative to sulfuryl fluoride gas: (1) the reagent must demonstrate comparable or improved reactivity to sulfuryl fluoride gas; (2) it must be a crystalline, shelf-stable and easily manipulated solid; and (3) it must be readily accessible for manufacturing on a large scale from commercially available starting materials.

AISF is a stable, crystalline solid that allows for a user-friendly fluorosulfonation reaction set-up, and it has excellent substrate scope. The reagent is easily manipulated in an open atmosphere and is stable at ambient temperature as either a solid or in solution, over a prolonged period of time.

"We are proud of this collaboration and our ability to address a common challenge in pharmaceutical preparation, delivering a solution that has a positive impact for both scientists and the environment," said Charlotte Allerton, Head of Medicine Design, Pfizer.

BioDuro is a leading, global life sciences research and development organization that provides biopharmaceutical clients and partners with comprehensive, fully integrated drug discovery services spanning target identification to IND filing, through to manufacture of drug substance for clinical trials. With depth and breadth of therapeutic expertise in small and large molecule discovery, development and scale-up, combined with unique technology platforms, such as high-content 3D drug screening and bioavailability enhancement of insoluble compounds, BioDuro is well positioned to help biopharmaceutical partners significantly accelerate their lead discovery programs, and de-risk development programs for higher value outcomes. For more information, visit www.bioduro.com.

Nuvaira Announces First Patient Treated in RELIEF-1 Study Evaluating New Approach for Asthma Treatment

Nuvaira recently announced treatment of the first patient in the RELIEF-1 Clinical Study in Europe. The RELIEF-1 trial (NCT02872298) is a prospective, multi-center, single-arm (non-randomized) study designed to evaluate the safety and technical feasibility of a procedure called Targeted Lung Denervation (TLD) using the Nuvaira Lung Denervation System for the treatment of severe asthma.

The feasibility study is slated to treat a total of 30 patients at facilities in France, Germany, the Netherlands, and the United Kingdom, with patient follow-up planned out to 3 years. Principal Investigators of RELIEF-1 are Nick ten Hacken, MD, PhD, at the University Medical Center Groningen (UMCG), the Netherlands, and Professor Pallav Shah, MD, at Royal Brompton & Harefield NHS Foundation Trust and Chelsea and Westminster Hospital NHS Foundation Trust in London. Dirk-Jan Slebos, MD, PhD, performed the first patient treatment in the Department of Pulmonary Diseases at UMCG.

"The first patient tolerated the minimally invasive therapeutic treatment very well, and there were no procedural complications," according to Dr. ten Hacken. "TLD is the first medical procedure that targets the whole lung by disrupting the overactive nerves into the lungs, thereby opening up the airways and making it easier to breathe. We are encouraged by how well the first patient responded to TLD and we look forward to treating additional asthma patients utilizing this innovative, one-time procedure."

The Nuvaira Lung Denervation System is a catheter-based system developed to treat patients with obstructive lung disease, specifically severe asthma and chronic obstructive pulmonary disease (COPD). The system's proprietary technology delivers targeted energy to disrupt nerve signals to the lungs using a process known as denervation. The simple, one-time bronchoscopic treatment has the potential to provide lasting whole lung improvement for severe asthma patients by opening obstructed airways to make breathing easier. Currently, there is no cure for asthma, but there are treatment plans that can help patients manage the disease. Approximately three quarters of asthma sufferers are adults, with 10% suffering from severe asthma, which is difficult to treat.

"The first patient treatment in our RELIEF-1 Clinical Trial is an important milestone in our quest to develop a safe and effective treatment for asthma patients worldwide," said Dennis Wahr, MD, Chief Executive Officer at Nuvaira. "Earlier trials evaluating TLD in COPD patients have demonstrated feasibility and promising long-term, sustained treatment results. We look forward to the completion of this important study."

Nuvaira (formerly known as Holaira) is a privately held company headquartered in Minneapolis, MN. The company is developing the Nuvaira Lung Denervation System to address chronic obstructive pulmonary disease (COPD) and asthma by treating the overactive airway nerves during Targeted Lung Denervation (TLD).

Organovo Division Samsara Sciences Announces Multi-Year Supply Agreement With Lonza Bioscience Solutions

Organovo Holdings, Inc. recently announced its wholly owned subsidiary, Samsara Sciences, Inc., a provider of highly specialized human liver cells, entered a non-exclusive global supply agreement with Lonza Bioscience Solutions. Under the terms of the agreement, Lonza will market human cell products from Samsara for further distribution to its customers.

"We're incredibly pleased to begin this partnership with Lonza, which allows us to tap into their outstanding global sales and marketing capabilities and expand the reach of our human cell products," said Dr. Sharon Presnell, President, Samsara and Chief Scientific Officer, Organovo. "This agreement, which represents Samsara's single largest contract to date, continues to establish Samsara as an emerging leader in the production and delivery of specialty human liver cells for use by biopharma clients in their research programs. Samsara has more than doubled its sales throughout the past year, and we expect that growing demand for our library of well-characterized healthy and disease-origin cells will continue to provide attractive revenue opportunities for our business."

"Organovo's mission to revolutionize how new therapies are discovered, tested, and ultimately delivered to patients begins with high-quality donor cells that are both the building blocks of our complex 3D tissues, and are also foundational elements in our client's research programs," said Taylor J. Crouch, CEO, Organovo. "We're seeing great commercial traction from this segment of our business, and believe it will become a bigger contributor to our revenue mix as we look ahead to fiscal 2019. We expect the Lonza agreement will accelerate the commercial penetration of our cell products in the global biopharma, academic, and research markets. In addition to boosting our top-line growth, Samsara's leading cell products also continue to support our own R&D mission, including our liver tissue disease-modeling platforms for non-alcoholic steatohepatitis (NASH) and fibrosis, as well as our NovoTissues IND-track liver therapeutic program for the treatment of alpha-1 antitrypsin deficiency."

Organovo is developing and commercializing a platform technology to produce and study living tissues that emulate key aspects of human biology and disease for use in drug discovery, clinical development, and therapeutic applications. The company develops tissue systems through internal research programs and in collaboration with pharmaceutical, academic, and other partners. Organovo's living tissues have the potential to transform the drug discovery process, enabling treatments to be developed more effectively and with greater relevance to performance in human trials and commercialization. The company's ExVive Liver and Kidney Tissues are used in disease modeling for NASH and fibrosis, high-value drug profiling, target and marker discovery/validation, and other drug testing. The company is also advancing a preclinical program to develop its NovoTissues liver therapeutic tissues for critical unmet medical needs, including certain life-threatening pediatric diseases.

MedPharm Receives Growth Equity Investment From Ampersand Capital Partners

MedPharm Ltd., a leading provider of contract topical and transdermal product design and formulation development services, recently announced a multi-million dollar investment by Ampersand Capital Partners.

Since its founding almost 20 years ago, MedPharm has established itself as a trusted developer of topical and transdermal products for the pharmaceutical drug development communities worldwide. The company's services currently encompass formulation development, performance testing, and clinical trials manufacturing at its facilities in Guildford, UK, and Durham, NC.

MedPharm's founders, Dr. Andrew Muddle and Prof. Marc Brown, will remain with the company to work with its growing executive team to expand MedPharm's service offering in topical and transdermal pharmaceutical development and manufacturing, as well as increase international CDMO market coverage whilst maintaining the company's long-established scientific principles and ethos.

Dr. Andrew Muddle, Co-founder and CEO of MedPharm, said "We are excited to partner with Ampersand to diversify MedPharm's service offering and regional coverage. We look forward to growing the business together for the benefit of our customers."

Professor Marc Brown, Co-founder and CSO of MedPharm, added "We have chosen to partner with Ampersand at an opportune time. Ampersand's investment will help us respond to strong market demand for MedPharm's services whilst maintaining our core values of scientific integrity, innovation and flexibility."

Ampersand General Partner David Parker also added "MedPharm is an excellent fit with Ampersand's strategy of investing in growth-oriented businesses that have established leadership positions in specialty segments of the CDMO market. We are thrilled to have the opportunity to partner with MedPharm's management team to drive future growth and success of the business."The actual sum of the investment was not disclosed

MedPharm Ltd. is a leading, global provider of contract topical and transdermal product design and formulation development services. MedPharm are experts at reducing risk and accelerating development times for generic and proprietary pharmaceutical customers through proprietary, industry-leading performance testing models. Well-established as a global leader in dermatology, nail, mucosal membrane, and transdermal product development, MedPharm also offers innovative solutions for ophthalmic and airway preparations. These solutions are recognized for their scientific rigor by regulators and investors. MedPharm has fully established R&D centres in the US and U.K. and GMP clinical manufacturing at its global headquarters facility in Guildford, UK. For more information, visit www.medpharm.com.

Founded in 1988, Ampersand is a middle market private equity firm dedicated to growth-oriented investments in the healthcare sector. With offices in Boston and Amsterdam, Ampersand leverages its unique blend of private equity and operating experience to build value and drive superior long-term performance alongside its portfolio company management teams.

Krystal Submits IND Application for Topical Gene Therapy Candidate

Krystal Biotech Inc. recently announced the submission of an IND application with the US FDA to initiate a Phase 1/2, first in-human trial of KB103, an HSV-1-based gene therapy engineered to deliver a human collagen-producing gene to patients with Dystrophic Epidermolysis Bullosa (DEB).

DEB is an incurable, often fatal, skin blistering disease caused by a lack of collagen protein in the skin. Krystal's approach is to use a non-replicating, non-integrating engineered HSV-1 virus, to deliver COL7A1 genes to dividing and non-dividing skin cells, causing them to produce the collagen protein. KB103 is designed to be an off-the-shelf treatment for DEB that can be applied as needed, either intradermally or topically, directly to a patient's skin.

"KB103 has the potential to become a first-in-class "off-the-shelf" topical gene therapy treatment for DEB. It is the result of an extensive research and preclinical effort by our internal team that included engineering, screening, and testing a library of in-house constructed vectors and complementing cell lines. This reflects our deep expertise in our proprietary Skin Targeted Delivery Platform (STAR-D)," said Suma Krishnan, Founder and Chief Operating Officer of Krystal. "As we look ahead, we believe that the productive STAR-D platform and our intent to bring GMP manufacturing in-house by the end of 2018 will support rapid advancement of clinical programs to treat debilitating skin diseases."

KB103 is Krystal's lead product candidate, currently in preclinical development and seeks to use gene therapy to treat dystrophic epidermolysis bullosa, or DEB, an incurable skin blistering condition caused by a lack of collagen in the skin. KB103 is a replication-defective, non-integrating viral vector that has been engineered employing Krystal's STAR-D platform to deliver functional human COL7A1 genes directly to the patients' dividing and non-dividing skin cells. HSV-1 is Krystal's replication-deficient, non-integrating viral vector that can penetrate skin cells more efficiently than other viral vectors. Its high payload capacity allows it to accommodate large or multiple genes and its low immunogenicity makes it a suitable choice for direct and repeat delivery to the skin.

Krystal's Skin TARgeted Delivery platform, or STAR-D platform, is a proprietary gene therapy platform consisting of an engineered viral vector and skin-optimized gene transfer technology that Krystal is employing to develop off-the-shelf treatments for dermatological diseases for which there are no known effective treatments. The company believes that the STAR-D platform provides an optimal approach for treating dermatological conditions due to the nature of the HSV-1 viral vector it has created. Certain inherent features of the HSV-1 virus, combined with the ability to strategically modify the virus in the form employed as a gene delivery backbone, provide the STAR-D platform with several advantages over other viral vector platforms for use in dermatological applications.

Dystrophic epidermolysis bullosa, or DEB, is an incurable, often fatal skin blistering condition caused by a lack of collagen protein in the skin. It is caused by mutations in the gene coding for type VII collagen, or COL7, a major component of anchoring fibrils, which connect the epidermis to the underlying dermis, and provide structural adhesion between these skin layers in a normal individual. The lack of COL7 in DEB patients causes blisters to occur in the dermis as a result of separation from the epidermis. This makes the skin incredibly fragile, leading to blistering or skin loss at the slightest friction or knock. It is progressive and incredibly painful.

The most severe form of DEB is recessive DEB, or RDEB, which is caused by null mutations in the COL7A1 gene. DEB also occurs in the form of dominant DEB, or DDEB, which is considered to be a milder form of DEB. There are no known treatments affecting the outcome of either form of the disease, and the current standard of care for DEB patients is limited to palliative treatments.

2017

Global Drug Delivery & Formulation REPORT

Notable Product Approvals of 2017

Part 2 of a 4-Part Series

Part 1: A Global Review

Part 2: Notable Product Approvals of 2017

Part 3: Notable Transactions and Technologies of 2017

Part 4: The Drug Delivery and Formulation Pipeline

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

Introduction

What's more interesting, the forest or the trees? Studying both can provide important information and insight. It's the same with drug delivery and formulation products. In the first part of this series (March 2018 issue), we took a big picture look at 2017 approvals. In this second part, we look at the more interesting individual products approved last year.

When looking at 2017 approvals as a whole, things don't seem to be much different than 2016, or the previous years. The drug delivery and formulation forest, it seems, has stopped evolving. That has been the case for the better part of a decade.

But if you look closely, one finds a new "species," gene/cell therapy products, among the expected injectable, oral, and inhalation product approvals. Whether these 2017 gene/cell therapy products are drug delivery or formulation enhanced is debatable. There is no question they will be. First-generation products always receive the attention of drug delivery and formulation to optimize therapeutic performance and create competitive advantage. The real question is whether this challenge will be taken up by the current generation of Drug Delivery and Formulation Professionals.

The Notable Product Approvals of 2017 are divided into three groups – Notable Drug Delivery & Formulation Approvals, Notable Drug-Device Approvals, and Other Notable Approvals. That last group includes the gene/cell therapy approvals.

Individual approvals, if looked at closely, can provide important insight into the development, health, and future of the larger forest.

Notable Drug Delivery & Formulation Approvals of 2017

Vantrela ER

Company: Teva (Cephalon)
Active(s): Hydrocodone Bitartrate
Molecule Type: Small Molecule
Indication: Pain Management
Delivery Route: Oral
Dosage Form: Oral Tablet
DD Category: Abuse Resistant Oral, Oral Barrier Film & Microparticles
Dosing: Twice Daily
First Approval: 2017-01-17 (USA)
Technology/Provider: OraGuard/Cima Labs (Teva)
Review Status: Standard, New Dosage Form – Discontinued (FDA)
Clinical Development/Approval Time: >7.2 Years
Notable: Approved yesterday and gone today. Vantrela ER was approved in January 2017, had its REMS proposal approved in May, and as of today is listed by the FDA as Discontinued. No reasons have been provided. With the ongoing concern about an opioid epidemic, it may be that companies are deciding that the commercial rewards do not outweigh the possible regulatory and public relations risks. Both Purdue Pharma (Hysingla ER) and Pernix (Zohydro ER) have previously introduced abuse-deterrent extended-release formulations of hydrocodone, so Vantrela ER would have been third to market with no obvious benefits.

Roxybond

Company: Daiichi Sankyo/Inspirion Delivery Sciences
Active(s): Oxycodone
Molecule Type: Small Molecule
Indication: Pain Management
Delivery Route: Oral
Dosage Form: Oral Tablet
DD Category: Abuse Resistant Oral, Oral Barrier Film & Microparticles
Dosing: Four to Six Times Daily
First Approval: 2017-04-20 (USA)
Technology/Provider: SentryBond/Inspirion Delivery Services
Review Status: Priority, New Formulation (FDA)
Clinical Development/Approval Time: >7.5 Years
Notable: Another abuse-deterrent formulation of oxycodone with a bit of a twist, an immediate-release presentation. Unlike Egalet's Oxaydo, Roxybond does not incorporate aversive agents, relying on physical formulation properties to counter attempts to powder and insufflate or inject the product. There are no available forecasts for Roxybond. Egalet's Oxaydo reported sales of $8 million in 2017.

Arymo ER

Company: Egalet
Active(s): Morphine Sulfate Pentahydrate
Molecule Type: Small Molecule
Indication: Chronic Pain
Delivery Route: Oral
Dosage Form: Oral Tablet
DD Category: Oral Erodible MR, Abuse Resistant, Oral
Dosing: Twice/Three Times Daily
First Approval: 2017-01-19 (USA)
Technology/Provider: Guardian / Egalet
Review Status: Standard, New Formulation (FDA)
Clinical Development/Approval Time: >3.8 Years
Notable: Arymo ER is another product in the increasingly long list of recent approvals for abuse-deterrent versions of well-characterized opioids, in this case morphine. It's not clear how physicians and formularies will embrace an abuse-deterrent formulation of a product that is not generally considered a first choice for abuse in the face of generic competitors. Arymo ER uses a physical approach to abuse deterrence that eliminates the issues seen with other morphine abuse-deterrent products that incorporate an opioid antagonist. Analysts estimate Arymo ER potential sales of $100 million by 2022.

Rebinyn

Company: Novo Nordisk
Active(s): Nonacog Beta Pegol
Molecule Type: Protein
Indication: Hemophilia B
Delivery Route: Injection
Dosage Form: Lyophilized Powder for Solution
DD Category: Prodrugs PEG Polymer, Reconstitution Systems
Dosing: Once Weekly
First Approval: 2017-05-31 (USA)
Technology/Provider: GlycoPEGylation Technology/Novo Nordisk, MixPro/Novo Nordisk
Review Status: Standard, BLA (FDA)
Clinical Development/Approval Time: >7.7 Years
Notable: The pipeline of innovative PEGylated products has shrunk over the past 2 decades as many opportunities have been previously captured or eliminated by virtue of longer half-life actives. Rebinyn is a 40 kD PEGylated version of recombinant Factor IX. In terms of presentation, it is only available as a lyophilized single-dose vial for reconstitution. The product is approved for acute use only. Analysts estimate global sales on the order of $150 million by 2023.

Cotempla XR-ODT

Company: Neos Therapeutics
Active(s): Methylphenidate
Molecule Type: Small Molecule
Indication: ADHD
Delivery Route: Oral
Dosage Form: Oral Tablet
DD Category: Conventional Melt Tablets, Taste Masking, Oral Ion Exchange MR
Dosing: Once Daily
First Approval: 2017-06-19 (USA)
Technology/Provider: Neos RDIM/Neos Therapeutics
Review Status: Standard, New Dosage Form (FDA)
Clinical Development/Approval Time: >4.2 Years
Notable: The ADHD market has largely escaped the attention of regulators and the public in terms of potential abuse liability. This has encouraged companies to develop differentiated product formulations. Cotempla XR-ODT is a 12-hour extended-release melt tablet formulation of methylphenidate. There is no evidence that Neos is developing a liquid methylphenidate formulation comparable to their Adzenys ER. Analysts forecast annual sales reaching $80 million by 2022.

Adzenys ER

Company: Neos Therapeutics
Active(s): Levamphetamine, Dextroamphetamine
Molecule Type: Small Molecule
Indication: ADHD
Delivery Route: Oral
Dosage Form: Oral Suspension
DD Category: Oral Liquid MR, Oral Ion Exchange MR, Taste Masking
Dosing: Once Daily
First Approval: 2017-09-15 (USA)
Technology/Provider: Neos DTRS/Neos Therapeutics
Review Status: Standard, New Dosage Form (FDA)
Clinical Development/Approval Time: >4 Years
Notable: The ADHD market has largely escaped the attention of regulators and the public in terms of potential abuse liability, leading companies to develop differentiated product formulations. Adzenys ER is the third Neos approval for ADHD. This once-daily liquid extended-release amphetamine formulation uses the same technology as Neos' Adzenys XR-ODT amphetamine product, in a liquid formulation. Analysts are suggesting the product will have modest annual sales that reach $30 million by 2022.

Mavenclad

Company: Merck Serono Europe
Active(s): Cladribine
Molecule Type: Small Molecule
Indication: Multiple Sclerosis, Relapsing Remitting
Delivery Route: Oral
Dosage Form: Oral Tablet
DD Category: Cyclodextrins/Solubilizers
Dosing: Single Dose Daily According to Protocol
First Approval: 2017-08-25 (EU)
Technology/Provider: Ivax/Teva Cyclodextrin-Complexes/Teva Pharmaceutical Industries
Review Status: Standard (EMA)
Clinical Development/Approval Time: >12.3 Years
Notable: Approved as far back as 1993 as an injectable for the treatment of a variety of hematological malignancies, cladribine has been reformulated as an oral treatment for highly relapsing multiple sclerosis. Dosing is unique with a recommended dose of 3.5 mg/kg (245 mg/70kg) over a 2-year period. An initial filing in 1997 by Ortho-Clinical was rejected. Some 20 years later, it is now approved in Europe, Australia, and Canada. The product is in Phase 3 development in the USA, after a 2011 rejection by the FDA. Sales are expected to grow to $200 million annually by 2022.

Mydayis

Company: Shire/Supernus
Active(s): Mixed Amphetamines
Molecule Type: Small Molecule
Indication: ADHD
Delivery Route: Oral
Dosage Form: Oral Capsule
DD Category: Oral Barrier Film & Microparticles, Oral Enteric/Delayed Release
Dosing: Once Daily
First Approval: 2017-06-20 (USA)
Technology/Provider: None
Review Status: Standard, New Dosage Form (FDA)
Clinical Development/Approval Time: >13.3 Years
Notable: The ADHD market has largely escaped the attention of regulators and the public in terms of potential abuse liability. This has led companies to develop differentiated product formulations. Shire, with its substantial ADHD market presence announced approval of Mydayis, another once-daily amphetamine product approval in June of last year. The product is distinguished by a longer duration of action, up to 16 hours. Analysts are relatively bullish on the product, estimating sales exceeding $400 million annually by 2022.

Zilretta

Company: Flexion Therapeutics
Active(s): Triamcinolone Acetonide
Molecule Type: Small Molecule
Indication: Osteoarthritis
Delivery Route: Injection
Dosage Form: Injection Powder for Suspension
DD Category: Biodegradable PLGA Microcaps/Implants
Dosing: Single Dose
First Approval: 2017-10-06 (USA)
Technology/Provider: Flexion PLGA Microspheres/Flexion Therapeutics
Review Status: Standard, New Formulation (FDA)
Clinical Development/Approval Time: >5.3 Years
Notable: Zilretta represents a logical therapeutic option for a common use of corticosteroids; intra-articular injection of the knee for the treatment of osteoarthritis. In this case, triamcinolone is formulated with biodegradable PLGA to provide a 4-fold extension of half-life. This appears to be the first long-acting steroid to be approved for this indication. Analysts are estimating annual sales reaching almost $500 million annually by 2022. Sometimes simple solutions to common problems can be profitable.

Lyrica CR Tablets

Company: Pfizer
Active(s): Pregabalin
Molecule Type: Small Molecule
Indication: Neuropathic Pain, Post-Herpetic Neuralgia
Delivery Route: Oral
Dosage Form: Oral Tablet
DD Category: Gastro Retentive, Oral Matrix MR
Dosing: Once Daily
First Approval: 2017-10-11 (USA)
Technology/Provider: Pfizer/Internal
Review Status: Standard, New Formulation (FDA)
Clinical Development/Approval Time: >7.0 Years
Notable: Pfizer has extended their significant Lyrica franchise with the approval of a once-daily formulation of pregabalin to combat impending generics. The product uses gastro-retentive and oral matrix modified-release technologies to move from twice daily to once daily. 2017 also saw the approval of Lyrica OD in Japan, an ODT twice-daily formulation of pregabalin to improve compliance for elderly patients with fibromyalgia.

Sublocade

Company: Indivior
Active(s): Buprenorphine
Molecule Type: Small Molecule
Indication: Opioid Dependence
Delivery Route: Injection
Dosage Form: Injection Solution
DD Category: Biodegradable Gel/Suspension
Dosing: Up to 6 Months
First Approval: 2017-11-30 (USA)
Technology/Provider: ATRIGEL/Tolmar, Novelion Therapeutics, RB Group
Review Status: Priority, Orphan, New Dosage Form (FDA)
Clinical Development/Approval Time: >7.1 Years
Notable: Faced with branded and generic competitors to their sublingual buprenorphine opioid dependence franchise, Indivior has added a long-acting depot formulation of buprenorphine for the same indication. It's not clear how physicians and patients will respond to this treatment option. Analysts have Sublocade annual sales reaching $800 by 2023, but Titan's 6-month Probuphine buprenorphine implant is apparently experiencing significant commercial and regulatory challenges. Perhaps an injection rather than an implant will make all the difference.

Oncaspar

Company: Baxalta (Shire)
Active(s): Asparaginase
Molecule Type: Protein
Indication: Acute Lymphocytic Leukemia
Delivery Route: Injection
Dosage Form: Lyophilized Powder for Solution
DD Category: Prodrugs PEG Polymer
Dosing: Once every 2 weeks
First Approval: 2017-12-13 (EU)
Technology/Provider: 1st Generation PEGylation / Enzon
Review Status: Standard (EMA)
Clinical Development/Approval Time: Unknown
Notable: Oncaspar has been a mainstay of pediatric ALL treatment for almost 3 decades. During much of that period, there have been periodic supply issues related to the availability of the asparaginase enzyme, and product stability issues. The development of a more stable formulation will go a long way to improving access. In the case of a hospital-administered product, the extra step of reconstitution is a small inconvenience for a secured supply of this life-saving drug. Analysts expect annual sales of Oncaspar to grow to more than $250 million by 2022.

Notable Drug-Device Approvals of 2017

Instanyl Doseguard

Company: Takeda Pharma, Nycomed
Active(s): Fentanyl Citrate
Molecule Type: Small Molecule
Indication: Breakthrough Pain
Delivery Route: Nasal
Dosage Form: Nasal Spray Metered
DD Category: Nasal Spray Pumps/Devices, Drug Delivery Compliance
Dosing: No less than 2 to 4 Hours
First Approval: 2017-05-15 (EU)
Technology/Provider: Aptar Nasal/SL Metered Dose eDevice/Aptar Pharma
Review Status: Standard (EMA)
Clinical Development/Approval Time: Unknown
Notable: Instanyl Doseguard represents a compliance enhancement to Instanyl, a nasal fentanyl formulation first approved in Europe in 2009. The device features a large and highly visible dose-counting display (number of doses left) and flashing display. The electronic display shows whether the nasal spray is locked or ready for use, and the "e-Lockout" feature counts and displays the number of actuations, preventing device actuation for a period of time after a pre-defined number of actuations.

Enbrel Mini Cartridge

Company: Amgen
Active(s): Etanercept
Molecule Type: Protein (Fusion)
Indication: Ankylosing Spondylitis, Juvenile Arthritis, Psoriasis, Psoriatic Arthritis, Rheumatoid Arthritis
Delivery Route: Injection
Dosage Form: Injection Solution
DD Category: Prodrugs Antibody- ADC, Autoinjectors, Reusable
Dosing: Once/Twice Weekly
First Approval: 2017-09-14 (USA)
Technology/Provider: AutoTouch/Amgen
Review Status: Supplement (FDA)
Clinical Development/Approval Time: Unknown
Notable: The Enbrel Mini Cartridge system has been designed as a follow on to the Prefilled Syringes and Pen presentations. The Enbrel Mini Cartridge is a single- use presentation that can only be used with the AutoTouch injector. The AutoTouch injector is intended to ensure more consistent dosing by limiting the number of potential points of patient confusion. AutoTouch and the Mini Cartridge system may be used as a platform for other Amgen products, including Neupogen, Nplate, and Aranesp.

Trelegy Ellipta Inhalation Powder

Company: Glaxo SmithKline
Active(s): Fluticasone Furoate, Umeclidinium Bromide, Vilanterol Trifenatate
Molecule Type: Small Molecules
Indication: Chronic Obstructive Pulmonary Disease
Delivery Route: Inhalation
Dosage Form: Inhalation Powder
DD Category: DPI-Dry Powder Inhalers, Combination/Incompatible
Dosing: Once Daily
First Approval: 2017-09-18 (USA)
Technology/Provider: Ellipta/Glaxo SmithKline
Review Status: Standard, New Formulation (FDA)
Clinical Development/Approval Time: >5.4 Years
Notable: Trelegy Ellipta represents a trifecta of sorts, providing COPD patients with a three-component therapy in a single inhalation, once a day. It's notable that the FDA approved the product as a New Formulation (Type 5) rather than either a New Dosage Form (Type 3) and/or New Combination (Type 4), suggesting that the approval was largely based on the previous approval of the separate two-component Ellipta products. Analysts expect sales to ramp up slowly, hitting $1 billion annually by 2022.

XHANCE

Company: OptiNose US
Active(s): Fluticasone Propionate
Molecule Type: Small molecule
Indication: Nasal Polyposis
Delivery Route: Nasal
Dosage Form: Nasal Spray Metered, Suspension
DD Category: Nasal Spray Pumps/Devices
Dosing: Once/Twice Daily
First Approval: 2017-09-18 (USA)
Technology/Provider: OptiNose Liquid Delivery Device/OptiNose US
Review Status: Standard, New Formulation (FDA)
Clinical Development/Approval Time: >5.2 Years
Notable: XHANCE is OptiNose's nasal polyposis product follow up to 2016's ONZETRA Xsail. XHANCE nasal spray incorporates the same unique delivery device that uses the patient's breath to power the nasal inhalation while closing the soft palate to limit dispersion of the dose. Restricting fluticasone to the sinus cavity is critical when dosing at 4-times the levels commonly prescribed with nasal steroids used for the treatment of seasonal allergies.

Bydureon BCise

Company: AstraZeneca
Active(s): Exenatide
Molecule Type: Peptide
Indication: Diabetes, Type 2
Delivery Route: Injection
Dosage Form: Injection Solution
DD Category: Biodegradable PLGA Microcaps/ Implants, Disposable Autoinjectors, Single Use
Dosing: Once Weekly
First Approval: 2017-10-20 (USA)
Technology/Provider: BCise/AstraZeneca
Review Status: Standard, Type-3
Clinical Development/Approval Time: >7.0 Years
Notable: Once-weekly dosing is not a competitive advantage if it requires the use of a clunky dual-chamber autoinjector. The new BCise autoinjector provides significant patient-use improvements over the older dual- chamber LyoTwist Trio device. Dose preparation time is reduced significantly, and the new BCise autoinjector better disguises the needle injection process. It increasingly seems that competition in the Type 2 diabetes market has become an "arms race" of ever improved formulations and injection devices. Bydureon BCise is expected to help grow the overall Bydureon franchise from $577 million in 2017 to almost $900 million by 2022.

Ozempic

Company: Novo Nordisk
Active(s): Semaglutide
Molecule Type: Peptide
Indication: Diabetes, Type 2
Delivery Route: Injection
Dosage Form: Injection Solution
DD Category: Injection Pens, Disposable
Dosing: Once/Twice Weekly
First Approval: 2017-12-05 (USA)
Technology/Provider: Flex Touch/Novo Nordisk
Review Status: Standard, New Molecular Entity (FDA)
Development/Approval Time: >10.5 Years
Notable: After a period of new outpatient injectables being introduced with a logical progression of vial/syringe presentations, followed by prefilled syringes, and then pen devices, products are increasingly being introduced with only an injection pen option. And dosing has moved from several times daily to once daily to once or twice weekly, significantly simplifying the treatment of Type 2 diabetes. Ozempic, it seems, will be major competition for Lilly's Trulicity. The real opportunity for semaglutide may be provided by an oral dosage formulation in Phase 3 trials. Ozempic annual sales are forecast to exceed $2.5 billion by 2022.

Abilify MyCite

Company: Otsuka Pharmaceutical
Active(s): Aripiprazole
Molecule Type: Small Molecule
Indication: Bipolar Disorder, Depression, Schizophrenia
Delivery Route: Oral
Dosage Form: Oral Tablet
DD Category: Drug Delivery Compliance, Ingestible Delivery Devices
Dosing: Once Daily
First Approval: 2017-11-13 (USA)
Technology/Provider: Proteus Ingestion Event Marker/Proteus Digital Health
Review Status: Standard, New Combination (FDA)
Development/Approval Time: >7.5 Years
Notable: Abilify MyCite combines the well-validated CNS agent aripiprazole with an ingestible sensor in an oral tablet presentation. The sensor tracks ingestion of the tablet by means of an external wearable patch that communicates the information to a smartphone application. The full potential for this type of medication-sensor combination is yet to be fully realized, but at this point, the major objective seems to track compliance, an issue with some psychiatric conditions. Sales are likely to be negligible, and will largely act as a test case for more commercially attractive opportunities.

Nyxoid

Company: Mundipharma International
Active(s): Naloxone Hydrochloride
Molecule Type: Small Molecule
Indication: Substance Abuse
Delivery Route: Nasal
Dosage Form: Nasal Spray
DD Category: Nasal Formulations
Dosing: Single Dose
First Approval: 2017-11-10 (EU)
Technology/Provider: None
Review Status: Standard (EMA)
Development/Approval Time: Unknown
Notable: Mundipharma's nasal naloxone was approved in Europe on the basis of a clinical literature review and a 5-part open label, randomized, single-dose, crossover study in healthy volunteers. The primary trial endpoints related to the Nyxoid's pharmacokinetic properties. In summary, a very limited investment to improve opioid overdose outcomes.

Other Notable Approvals of 2017

Vyxeos

Company: Celator Pharmaceuticals (Jazz Pharmaceuticals)
Active(s): Cytarabine, Daunorubicin
Molecule Type: Small Molecule
Indication: Acute Myelogenous Leukemia
Delivery Route: Injection
Dosage Form: Injection Lyophilized Powder for Suspension
DD Category: NP liposome, Combination/ Incompatible
Dosing: Per Protocol
First Approval: 2017-08-03 (USA)
Technology/Provider: CombiPlex Drug-Ratio Technology/Celator Pharmaceuticals
Review Status: Priority, Orphan, New Combination (FDA)
Clinical Development/Approval Time: >15.9 Years
Notable: Vyxeos uses Celator's Combiflex Drug-Ratio technology that identifies molar ratios of drugs that deliver a synergistic benefit and locks the desired ratio in a "nano-scale" liposomal drug delivery vehicle that maintains the ratio in patients. Using two well-characterized actives, cytarabine and daunorubicin, Vyxeos received Priority and Orphan designation from the FDA as a first-line treatment for AML, a very competitive indication. Analysts have forecast Vyxeos annual sales of more than $300 million by 2022.

Gene Cell Therapy

Kymriah

Company: Novartis/Univ. of Pennsylvania
Active(s): Tisagenlecleucel
Molecule Type: T-Cell
Indication:m Acute Lymphocytic Leukemia
Delivery Route: Injection
Dosage Form: Injection Suspension
DD Category: Retroviral Transfection, Cell Expansion
Dosing: Once Only
First Approval: 2017-08-30 (USA)
Technology/Provider: CART-19/Univ. of Pennsylvania
Review Status: Priority, BLA (FDA)
Clinical Development/Approval Time: >7.5 Years
Notable: CAR-T (Chimeric Antigen Receptor, T-cell) immunotherapies are the great hope for recruiting a patient's immune system to selectively recognize and attack cancer cells. At this stage, Kymriah is limited to patients up to the age of 25 with relapsed or refractory Acute Lymphoblastic Leukemia. Additional indications are in clinical development. Analysts forecast sales of more than $1 billion annually by 2022, mostly in Europe.

Yescarta

Company: Kite Pharma (Gilead Sciences)
Active(s): Axicabtagene Ciloleucel
Molecule Type: T-Cell
Indication: B-Cell Lymphomas, DLBCL, Follicular Lymphoma, NHL
Delivery Route: Injection
Dosage Form: Injection Suspension
DD Category: Retroviral Transfection, Cell Expansion
Dosing: Once Only
First Approval: 2017-10-18 (USA)
Technology/Provider: CAR/National Cancer Instituite
Review Status: Priority, Orphan, Breakthrough Therapy, BLA (FDA)
Clinical Development/Approval Time: >8.8 Years
Notable: CAR-T (Chimeric Antigen Receptor, T-cell) involves the tedious and costly process of transfecting the patient's T-cells ex vivo with a retroviral construct coding the specific CD-19 targeted antigen, expanding the cells and reinfusing them to the patient. At this stage, treatment is limited to relapsed or refractory patients with B-Cell Lymphomas, DLBCL, Follicular Lymphoma, or NHL. Analysts forecast Yescarta sales of more than $2 billion annually by 2022.

Luxturna Injection

Company: Spark Therapeutics
Active(s): Voretigene Neparvovec
Molecule Type: AAV Gene Vector
Indication: Leber's Congenital Amaurosis, Retinitis Pigmentosa
Delivery Route: Surgical Insertion
Dosage Form: Injection Suspension
DD Category: Adeno-Associated Virus Vectors
Dosing: Once Only
First Approval: 2017-12-19 (USA)
Technology/Provider: Spark AAV Vectors/ Children's Hospital of Philadelphia, Spark Therapeutics
Review Status: Priority, Orphan, Rare Pediatric, BLA
Clinical Development/Approval Time: >10.9 Years
Notable: This seems to be an ideal indication for early gene therapy to explore: a clear mechanism of action, a localized condition not amenable to traditional therapies, and one-time administration. It makes sense in terms of cause and effect, the need is high without options, and the potential for a life- threatening adverse event is limited. The expanded safety information that will be provided by commercial use of Luxturna may validate the use of the Spark AAV vector system for less localized applications. Despite the very limited indication, analysts have forecast annual sales of more than $500 million by 2022.


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PREFILLED SYRINGES

Prefilled Syringe Automated Inspection & End-Product Testing

By: Gregory A. Sacha, PhD

INTRODUCTION

Prefilled syringes are used for many therapeutic biologic formulations, and are a good option for ophthalmic injections that require very low volumes of the drug product.[1] They are useful for biologics and other expensive drug products because the overfill volume for the syringe is much lower than the volume required for products filled into vials. Another advantage of a prefilled syringe is their ease of use. They are suitable for self-delivery by the patient and reduce the risk of contamination when compared to the multiple steps required for withdrawing a dose from a vial. They are, however, challenging to manufacture with respect to filling, sealing, inspecting, and conducting testing that is specific to the primary packaging. Challenging operations for prefilled syringes that are not often discussed in the literature include automatic inspection and testing specific to the final product. Filled dosage units intended for parenteral administration must be inspected for visible particulates to the extent possible so that they are considered essentially free of particle contamination.[2-5] The filled units may undergo 100% manual inspection, semi-automated inspection, or fully automated inspection. There are specific requirements for conducting the inspection and the minimum intensity of light used for the inspection.[5] These requirements also apply when using fully automated inspection equipment.

There are additional requirements for end-product testing that are specific for prefilled syringes. For example, functionality tests are conducted to ensure proper movement of the plunger within the syringe barrel.[6,7] Container closure integrity testing is conducted to ensure there are no leaks that could affect the sterility assurance of the product.[8-11] The numerous requirements for product inspection and evaluation require expertise in working with the equipment as well as knowledge of the available methods for evaluation. This article introduces the common equipment available for automated inspection and discusses inspection testing methods for prefilled syringes.

TABLE 1

Company	Equipment
Bonfiglioli Engineering	PK-V Combi
Bosch Packaging Technology	Static Division System (SD)
Brevetti	K15-K15-600 and K15-C
Innoscan	Syringe Inspection Machine
Seidenader	VI-S

List of automated inspection equipment from different companies for use with prefilled syringes.

AUTOMATED INSPECTION

Different companies offer a variety of semi-automated and fully automated inspection equipment (Table 1). This provides many choices for companies in need of inspection equipment.

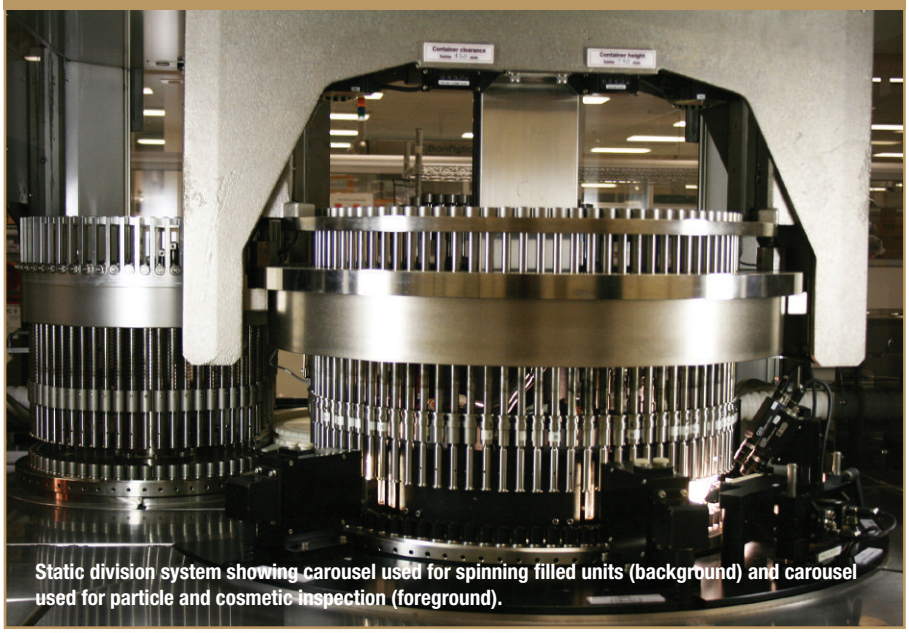
The fully automated inspection equipment operates using a vision detection system. Most are based on the static division system in which there is a light source in front of the syringe and a diode array detector located behind the syringe. The software tracks a voltage drop across a shadow that could be indicative of a particle or a defect. Syringes enter the machine and pass through two different carousels. One carousel spins the syringe or vial to create a vortex in the solution, and the second carousel completes the inspection (Figure 1). The syringes enter a carousel

and are held in place using tooling specifically designed for the size and type of syringe being inspected. Cosmetic defects and particle inspections are conducted on a single carousel equipped with two different inspection stations.

Syringes are inspected for particles after they are spun to create a vortex on the initial carousel. The vortex should cover the entire product-contact surface of the syringe barrel. The goal is to bring any particle that may be in the solution to the surface of the contents of the syringe and to do so without creating bubbles or foam. Particles will be detected if they block light transmitted through the syringe.[12] The challenge is that particles may not be detected if they are attached to the surface or ribs of the plunger or located within the cone of the syringe near the fluid path. Fortunately, it is rare to find particles located on the plunger or in the cone of the syringe, and they are often found by visual observation. Syringes that contain particles or fibers adhered to the surface of the syringe barrel will be rejected as cosmetic defects. Syringes that are rejected by the equipment are manually inspected to determine if they are truly a cosmetic defect or if foreign material is present in the syringe. An investigation may be initiated if rejected syringes appear with foreign material. The syringes are examined for cosmetic defects while on the same carousel immediately after inspection for particles.

Cosmetic defects are detected using a high-resolution camera and an image subtraction algorithm. The equipment is calibrated using syringes from a defect library. The defect library contains syringes exhibiting specific defects observed at the manufacturing site. These may include syringes with cracks or inclusions in the glass. They can also include syringes with cracked flanges, but many other possible defects exist. The defect samples are later used to challenge the equipment before and after inspection of each batch to ensure that the defects are identified by the equipment. The goal is for no more than one defect to be accepted. The set of cosmetic defects is based on the acceptable quality limit (AQL). The goal is to ensure that the number of false rejects does not exceed an established threshold percentage of the total defective units identified. Depending on the established threshold, the equipment would, for example, identify 98% of the defective units and have no more than 2% as false rejects. The equipment is qualified by introducing 10 defective units to the equipment along with 10 acceptable units. The number of acceptable units included for a test is increased after each successful inspection until 10 defective units can be identified in a batch of approximately 10,000 acceptable units. The process is labor intensive, requires close communication with customer support services for the equipment, and must be completed for each new product and different size or type of prefilled syringe.

FIGURE 1



Static division system showing carousel used for spinning filled units (background) and carousel used for particle and cosmetic inspection (foreground).

The syringes that pass automated inspection may proceed to automated container closure integrity testing (CCIT). Most equipment available for automated visual inspection can also be equipped with automated CCIT, such as high-voltage leak detection systems.

CONTAINER CLOSURE INTEGRITY TESTING (CCIT)

Minute cracks, pinholes, and needles that pierce the endcaps can be missed during the inspection process for prefilled syringes. The only way to ensure there is no risk to sterility assurance of the filled syringes is to test each one. Testing each filled unit was not possible before non-destructive, fully automatic testing instruments were invented. A variety of CCIT methods are now available. Chapter 1201.2 of the USP defines the methods as deterministic and probabilistic.[9] Deterministic methods are preferable and consist of non-destructive methods of testing making it possible to test each unit that was manufactured. Examples of the deterministic methods in-

"The shape of prefilled syringes and the small volumes they contain make them challenging to inspect for particles and cosmetic defects. Automated inspection systems greatly reduce the time needed for inspection and improve the detection of defects."

FIGURE 2

Example of an in-process, automated vacuum decay container closure integrity tester.

clude vacuum/pressure decay testing, high-voltage leak detection, and methods that utilize a laser to analyze the head space of a filled unit. There is also an instrument by Heuft™ called the Syringer® that uses x-ray pulses to identify syringes with bent needles and needles that puncture the caps. Vacuum/pressure decay, headspace analysis, and high-voltage leak detection methods are more common and are easily attached to a production line for 100% inspection (Figure 2).

The vacuum/pressure decay methods subject individual units to a preset vacuum or pressure and monitor for changes in the vacuum/pressure that can indicate a leak. The data can also be used to calculate the size of the leak. The method can be combined with a mass flow recorder to monitor the loss of headspace gas. This method is also referred to as a mass extraction method.

A laser can be used to examine the headspace of a filled unit using wave modulated near infrared spectroscopy or frequency modulated near infrared spectroscopy. The laser is directed through the headspace of the unit, and the data are compared against a set of standards. The standards are prepared based on the gas or on levels of water vapor that are being measured.

Most of the probabilistic methods for testing container closure integrity are destructive methods. They include bubble emission, microbial challenge, and tracer liquid testing.[9] The tracer gas detection method is a non-destructive probabilistic method. This method is typically used for packaging in which the package is exposed to helium for a certain amount of time. The package is removed and tested for the presence of helium that may be flowing from a leak in the packaging.

The bubble emission, microbial challenge, and tracer liquid test methods are conducted by immersing the filled units in water, in a concentrated bacterial suspension, or in a liquid that can be used as a tracer, such as a dye or metallic ions. Pressure is applied to the immersed units to provide a challenge. The units are examined for the emission of bubbles from a possible leak, microbial growth after incubation, or a color change or detection of the metal ions, respectively. The destructive nature of the tests prevents them from being used to test each unit. Samples are obtained randomly and tested together using one of the methods. This is typically conducted initially after manufacturing and then tested over time as part of a stability study.

FUNCTIONAL TESTING

Testing the performance of a prefilled syringe after filling and throughout the shelf-life is recommended.[13] Part of this testing includes glide force and break force testing. The break force is the energy required to initiate movement of the plunger

in the syringe barrel. The glide force is the energy required for the plunger to continuously move through the barrel of the syringe. It can be uncomfortable for the person delivering the dose and for the patient if excessive force is required to initiate movement of the plunger. Continuous, smooth, movement of the plunger through the barrel is desired. Incomplete coverage of the barrel with silicone oil or redistribution of the oil can cause the plunger to intermittently stop traveling the length of the barrel. This is referred to as "chattering" and can also be uncomfortable. Instruments for testing the break force and glide force are available and include instruments from Zwick/Roell™ and Instron™.

SUMMARY

The shape of prefilled syringes and the small volumes they contain make them challenging to inspect for particles and cosmetic defects. Automated inspection systems greatly reduce the time needed for inspection and improve the detection of defects. The inspection systems can often be combined with automated container closure integrity testers to ensure sterility of the entire batch. Expertise is needed for qualification and validation of the inspection equipment. Specific inspection criteria must be entered for each type of syringe inspected on the equipment. In addition, a library containing syringes with common defects is needed for qualification and testing of the equipment.

Prefilled syringes are routinely examined for functional performance as well as container closure integrity. Instruments are available for testing the force needed to initiate movement of the plunger and the force needed for movement of the plunger through the syringe barrel. The tests are often included in stability studies to ensure proper performance of the prefilled syringe over time. ◆

ACKNOWLEDGMENT

The author would like to thank Jason Hasler, Senior Validation Specialist, Baxter's Bloomington, IN, facility, for his contributions and knowledge of the inspection equipment.

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BIOGRAPHY

Dr. Gregory A. Sacha is a Senior Research Scientist in Research and Development at Baxter BioPharma Solutions with 18 years of experience in the pharmaceutical industry. Dr. Sacha currently leads a group of scientists in formulation and process development for parenteral products with a focus on the formulation of large molecules and lyophilization. His research interests include formulation variables affecting the stability of large molecules, thermal analysis of pharmaceutical formulations, and factors affecting scale-up of lyophilization processes. Dr. Sacha's list of publications includes topics in parenteral product packaging and prefilled syringes.

MONOCLONAL ANTIBODIES

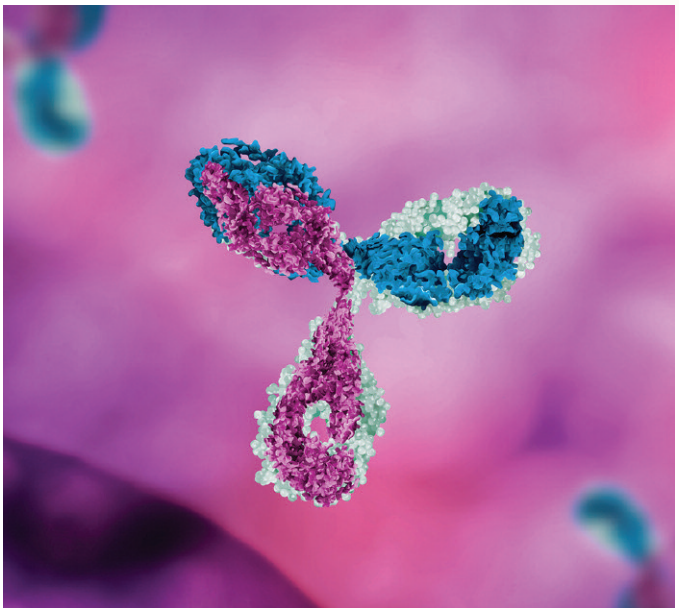
The Development of Therapeutic Monoclonal Antibody Products: A Comprehensive Guide to CMC Activities From Clone to Clinic

By: Howard L. Levine, PhD, and Brendan R. Cooney

INTRODUCTION

As the pharmaceutical market in the US and the rest of the world continues to expand, biopharmaceutical products have taken on increasing importance in the treatment of disease. Sales of monoclonal antibody products have grown from approximately $50 billion in 2010 to almost $90 billion in 2015, an approximately 1.8 fold increase, and represent nearly 58% of biopharmaceutical sales. As more and more exciting monoclonal antibody products for treatment of cancer, autoimmune diseases, cardiovascular disease, and other indications are introduced, sales from new products approved in the coming years will drive the world-wide sales of monoclonal antibody products to approximately $110 billion by 2018 and nearly $150 billion by 2021.

When The Development of Therapeutic Monoclonal Antibody Products was originally released in 2010, it quickly became an indispensable tool for those involved in the development or financing of monoclonal antibodies. It served as a guide to the complex technical, regulatory, and strategic Chemistry, Manufacturing, and Controls (CMC) activities necessary to successfully advance new monoclonal antibody products to clinical trials and the market as quickly as possible. This Second Edition has been fully revised and updated for 2017, to provide a roadmap for the development of a monoclonal antibody product from initial discovery through the filing of an Investigational New Drug Application (IND) or Investigational Medicinal Product Dossier (IMPD) or equivalent for first-in-human clinical trials. The primary



focus of the report remains on the technical, regulatory, and management issues related to process development, manufacturing, quality control, and analysis of full-length single specificity monoclonal antibody products produced in mammalian cell culture. New to the Second Edition is an in-depth look at Quality by Design (QbD) for monoclonal antibodies in an all new chapter, an entirely new perspective on cell line development and engineering, a fresh look at process validation in line with current regulatory requirement, and updates aligning the content with today's philosophies and practices throughout.

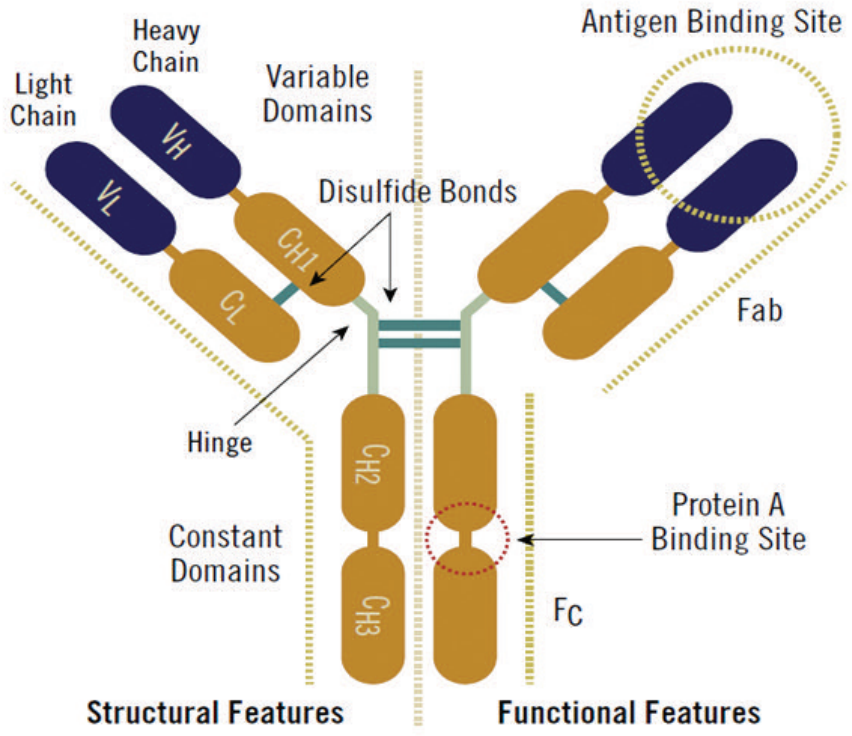
The Development of Therapeutic Monoclonal Antibody Products Second Edition goes beyond other reports by incorporating the latest technical developments and integrating strategic and

"As the pharmaceutical market in the US and the rest of the world continues to expand, biopharmaceutical products have taken on increasing importance in the treatment of disease. Sales of monoclonal antibody products have grown from approximately $50 billion in 2010 to almost $90 billion in 2015, an approximately 1.8–fold increase, and represent nearly 58% of biopharmaceutical sales. As more and more exciting monoclonal antibody products for treatment of cancer, autoimmune diseases, cardiovascular disease, and other indications are introduced, sales from new products approved in the coming years will drive the world-wide sales of monoclonal antibody products to approximately $110 billion by 2018 and nearly $150 billion by 2021."

regulatory considerations with these technical requirements. This report serves as a guide to product development companies, service providers, investors, and analyst as they work their way through the complex and rapidly evolving world of therapeutic monoclonal antibodies.

As shown in Figure 1, IgG antibodies usually have four inter-chain disulfide bonds, two connecting each light chain with a heavy chain and two connecting the heavy chains to enable dimerization. This feature of the Fc region of the heavy chain can be utilized to form dimers of other therapeutic proteins by creating a fusion between the protein of interest and the IgG heavy chain Fc sequence. Among the potential therapeutic benefits of these fusion proteins is a longer serum half-life of the fusion protein compared to the monomer used without linkage to the Fc region and bivalent functionality. Intra-chain disulfide bonds are also found in the variable and

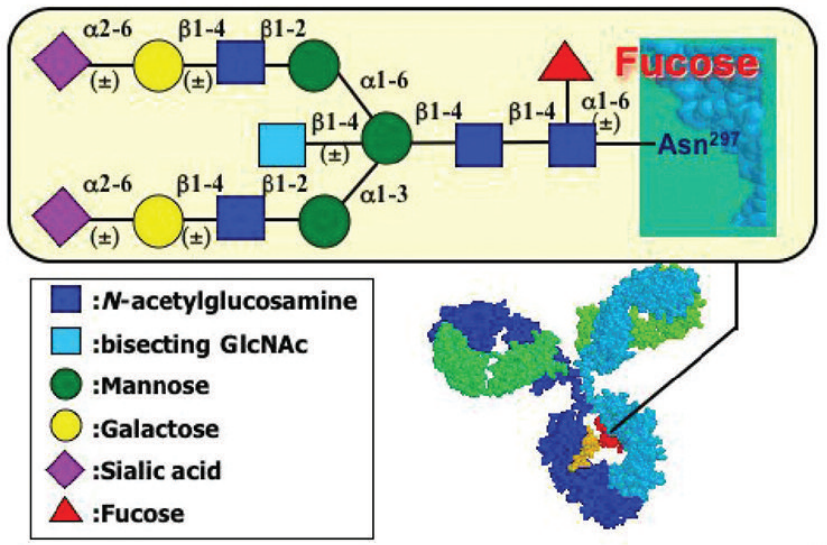
FIGURE 1



VH=heavy chain variable region; VL=Light chain variable region; CH1, CH2, CH3=Heavy chain constant regions, CL= Light chain constant region

Source: BPTC **Antibody Structure**

FIGURE 2



The oligosaccharide structure of N-linked glycans in the CH2 domains is shown. Individual sugar moieties may or may not be present in all molecules (indicated by ± in the figure), however sialic acid can only be present if galactose is also present in the oligosaccharide structure. (Figure adapted and reprinted with permission from References 14 and 15)

IgG Oligosaccharide Structure

Source: GlycoWord

constant regions. The intra-chain bonds in the variable regions help create the three dimensional structure that enables proper antigen binding. Low levels of free sulfhydryl groups from disulfide bonds that did not form properly can be found in recombinant antibodies and can create product stability problems.

ANTIGEN BINDING

The antigen binding function of an antibody is located within the 110 amino acid variable region at the N-terminus of each chain. Within the variable regions, three surface-exposed hypervariable amino acid loops, known as complementarity determining regions (CDR), are embedded in a relatively conserved framework structure. The six combined CDRs from the heavy and light chains form the antigen-binding site, and slight changes to CDR sequences can significantly alter affinity and specificity for the target antigen. Because the antigen-binding function of an antibody is localized in such a specific region of the protein, molecular engineering tools can be used to introduce novel variability in the CDRs of one or both chains followed by in vitro selection for improvements in target binding. Binding at the antigen-binding sites on each arm of the antibody can occur independently so that the antibody can also be engineered to contain two different antigen-binding domains. Such bi-specific antibodies are currently under development by several companies. In addition, if the variable region of an antibody is cloned independently and expressed as a soluble monomer, it will retain the ability to bind to the target antigen. These monovalent products are also under development by several companies.

EFFECTOR FUNCTIONS

In addition to antigen-binding function, antibodies contain oligosaccharides on the constant region that can interact with other components of the immune system to activate effector functions, such as antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). If immune system activation is important for the therapeutic activity of an antibody, the oligosaccharide structure is often critical to the clinical behavior of the molecule. For IgG antibodies, an N-linked biantennary oligosaccharide is attached to a highly conserved asparagine. The core structure contains three mannose residues and two N-acetyl-glucosamine residues (GlcNAc) as shown in Figure 1. In some monoclonal antibodies, the carbohydrate structure may also contain fucose. If present, the fucose residue is linked to the proximal GlcNAc residue, and additional terminal sugar residues, including galactose and sialic acid, are also present. Occasionally GlcNAc is added to the central mannose to form a structure known as a bisecting GlcNAc, which has a significant impact on antibody function.

Variation in the terminal sugar residues is the basis of most of the glycan heterogeneity seen in purified, recombinant monoclonal antibodies. This can influence which, if any, effector functions are activated. For example, the oligosaccha-

ride can contain either no (G0), one (G1), or two (G2) terminal galactose residues (Figure 2); increased galactose content can increases CDC activity while ADCC activation is not known to be affected by the galactose content of the oligosaccharide. Likewise, if fucose is not present on the core GlcNAc, the antibody exhibits enhanced ADCC activity compared to the fully fucosylated form but no impact on CDC has been observed. In addition, variation in the oligosaccharide structure in the binding protein of an Fc-fusion may greatly impact overall half-life in a way not generally seen with whole antibodies. For example, sialic acid content in the binding protein may greatly affect half-life or efficacy of the product. Glycan variability is primarily influenced by clone selection and cell culture conditions, but should also be considered during discovery and lead candidate identification, especially when choosing a heavy chain constant region for a particular target product profile. If effector functions are not required for the intended therapeutic mode of action, it may be most effective to develop an IgG4 antibody that has less effector function. For example, for monoclonal antibodies whose therapeutic activity is entirely based on blocking another protein from binding to the target, effector function and oligosaccharide structure are not critical to therapeutic function.

THERAPEUTIC APPLICATIONS OF MONOCLONAL ANTIBODIES

Following the approval of Orthoclone OKT3, there was a long gap before any new antibody products were approved. During this time, new approaches to discovering and developing antibody products emerged, and enthusiasm for therapeutic monoclonal antibodies returned. Several additional monoclonal antibody products were approved in the US and Europe in the mid to late 1990s, while the 2000s ushered in the next wave of antibody products generally being developed as anti-cancer and anti-inflammatory agents. Today, monoclonal antibody products, including fragments, conjugates, and full-length entities are a mainstay in the pharmaceutical industry. Utilizing today's novel technologies and enhanced targeting, they continue to be discovered, developed, and approved to treat many different diseases. As of October 31, 2016, there were 71 monoclonal antibody-related products on the market in the US and/or Europe for the treatment of a variety of diseases, including autoimmune disorders, cardiovascular indications, infectious diseases, and oncology. These approved monoclonal antibody products, which include full-length monoclonal antibodies as well as antibody fragments (Fab fragments), Fc-fusion proteins, antibody-drug conjugates, and other conjugated antibody products, have been approved for diseases with patient populations ranging from a few thousand or fewer for such orphan indications as paroxysmal nocturnal hemoglobinuria, or the cryopyrin-associated periodic syndromes, to hundreds of thousands of patients for some cancers and multiple sclerosis, to millions of patients for diseases, such as asthma and rheumatoid arthritis. ◆

This executive summary is based on the following market research report published by Insight Pharma Reports: The Development of Therapeutic Monoclonal Antibody Products Second Edition by Howard L. Levine, PhD, and Brendan R. Cooney. For more information, visit www.insightpharmareports.com

BIOGRAPHY

Dr. Howard L. Levine, President and CEO of BioProcess Technology Consultants, Inc. (BPTC), is a pioneer and thought leader in the biopharmaceutical industry with extensive strategic and operational experience in biopharmaceutical product development and commercialization. In his more than 35 years in the biopharmaceutical industry, he has assisted numerous companies in developing biological products, provided strategic input in the development of new manufacturing technologies, and participated in the successful commercialization of several of these products. Prior to founding BioProcess Technology Consultants in 1994, Dr. Levine was Vice President of Manufacturing Operations at Repligen Corporation and previously held positions of increasing responsibility in process development and manufacturing at Genentech, Amgen, and Xoma.

Brendan R. Cooney, Associate Consultant of BioProcess Technology Consultants, Inc., has more than 8 years of experience as a technical and science writer in the pharmaceutical industry and academia. He has been involved in developing and writing document guidance systems and internal documentation systems for both research and commercial applications. Prior to working for BioProcess Technology Consultants, he founded and ran CBRC Consulting, which provided technical writing consulting services to biotech companies, including Shire HGT and Histogenics Corporation. He earned is BA (magna cum laude) from Northeastern University in Boston, MA.

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BUSINESS APPLICATIONS

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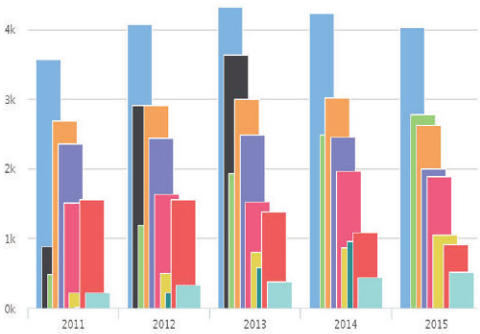
- Review comparable deals, acquisitions and financings
- Find and compare contract manufacturers and other outsourced services
- Assess competitive landscapes around an indication and research competitor pipelines
- Track generics and biosimilars, and identify Rx to OTC switch opportunities



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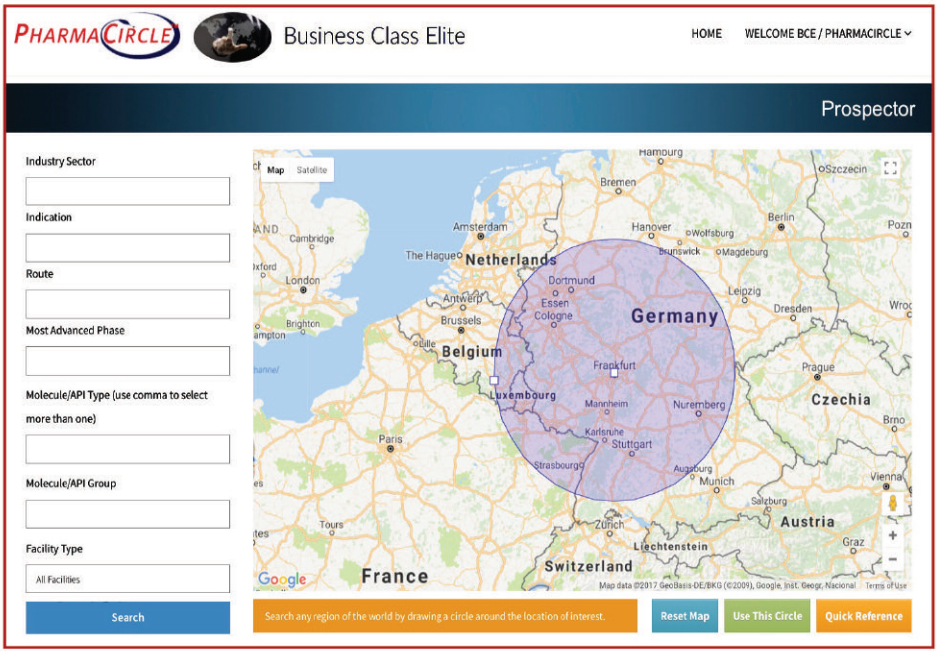

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ORALLY INHALED PRODUCTS

Optimizing the Application of *In Vitro* Test Methods for the Demonstration of Bioequivalence in Orally Inhaled Products

By: Mark Copley, MEng, and Anna Sipitanou, MSc

INTRODUCTION

Orally Inhaled Products (OIPs) are a commercially compelling target for generic development, with the combined annual revenues of key products, such as Seretide®, Spiriva®, and Symbicort® in the region of $10 billion.[1] Diseases of the respiratory system account for 8% of all deaths in the EU, driving demand for treatments that are safe, efficacious, and cost effective. Replicating the performance of an OIP and demonstrating bioequivalence (BE) is complex, largely because OIP behavior is a function of interactions between the patient, device, and formulation. Ensuring the development of an optimal approach to the demonstration of BE is an important step in accelerating safe and effective generic products to market.

Demonstrating BE in any generic product typically relies on a combination of *in vitro*, pharmacokinetic (PK) and pharmacodynamic (PD) studies, though *in vitro* studies alone may be sufficient for certain products. For OIPs, there is ongoing debate as to the relevance of these different tests, and the Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance differs in this regard. Reducing requirements for PK and/or PD studies is an attractive proposition because *in vitro* testing is typically the least expensive option. Maximizing the clinical relevance of *in vitro* test methods – an important and ongoing theme in OIP research – supports this goal.

The following examines the testing strategies demonstrating the BE of OIPs, their relevance, and the submission approaches outlined by the FDA and EMA. A key focus is the application of *in vitro* test methods and how these can be modified beyond the standard tests developed primarily for quality control (QC), to give improved *in vitro in vivo* correlations (IVIVCs) that are more useful for BE studies.

TESTING FOR BE

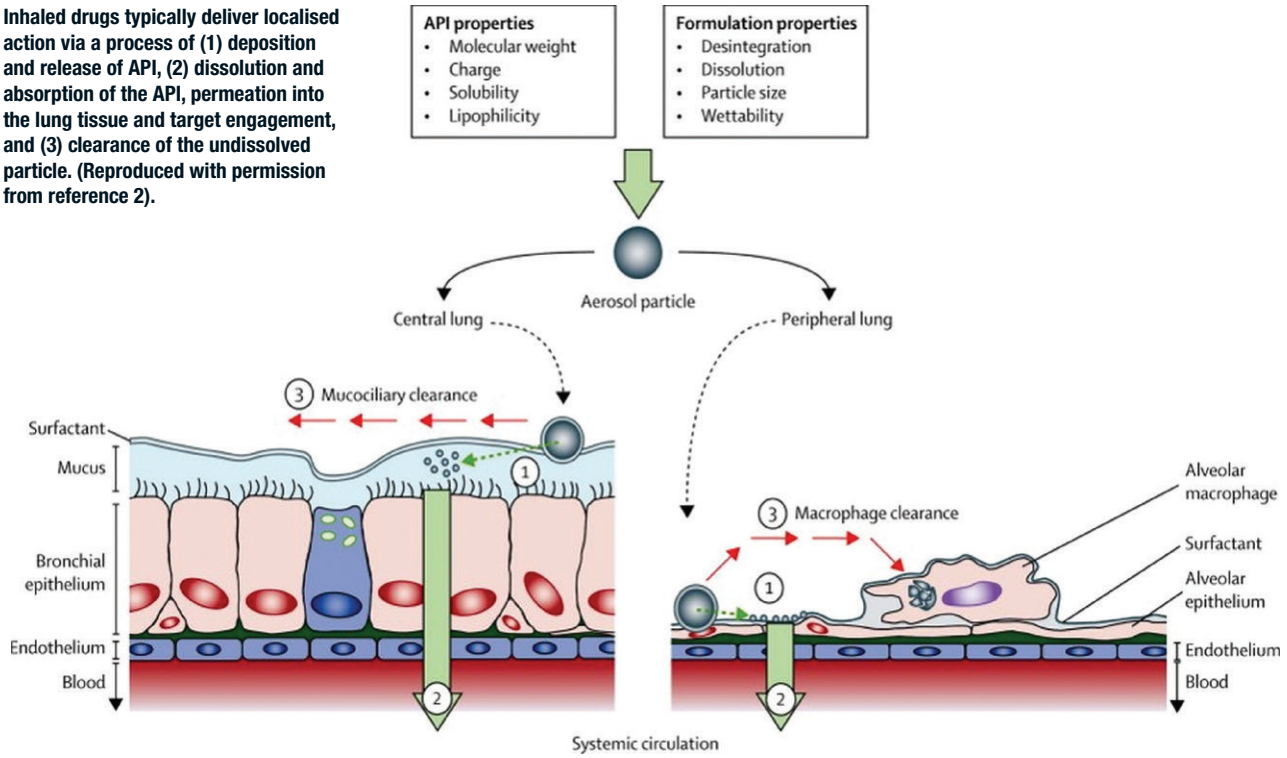
A generic product is prescribed interchangeably with the reference product and must therefore deliver closely equivalent clinical efficacy. *In vitro* tests, PK and/or PD studies are all routinely used to support claims of BE between a test (T) and reference (R) product, but differ markedly in terms of their: Complexity, Practicality, Discriminating Power, Clinical Relevance, and Cost.

Assessing how inhaled drugs reach the lung and achieve therapeutic action helps to elucidate the relevance, value, and limitations of these different testing strategies, and highlights the unique difficulties associated with demonstrating BE between OIPs.

During inhalation, aerosolized particles are drawn from the OIP through the oropharyngeal region, into the main airways of the lung, and potentially into the deep lung. An upper size limit of 10 microns is typically assumed for penetration into the upper airways and 5 microns for deposition in the deep lung, with coarser particles depositing in the mouth/throat and likely entering the bloodstream via the gastrointestinal (GI) tract. When de-

FIGURE 1

Inhaled drugs typically deliver localised action via a process of (1) deposition and release of API, (2) dissolution and absorption of the API, permeation into the lung tissue and target engagement, and (3) clearance of the undissolved particle. (Reproduced with permission from reference 2).



posited in the deep lung, inhaled drug particles dissolve in the limited quantities of fluid that line the lungs, although mucociliary clearance (MCC) mechanisms simultaneously act to flush the particles from the body. Permeation into the lung tissue brings the dissolved drug into contact with its intended target, enabling localized binding and therapeutic action. Any drug absorbed through the lung tissue enters into systemic circulation (Figure 1).

In vitro test methods are used to quantify a number of metrics directly associated with OIP efficacy. Core tests include the amount of drug delivered under standardized/well-controlled conditions – delivered dose uniformity (DDU) – and the aerodynamic particle size distribution (APSD) of that dose, which is measured using cascade impaction and influences *in vivo* deposition behavior. Other tests may include spray plume and plume geometry measurements, in the case of metered-dose inhalers (MDIs).

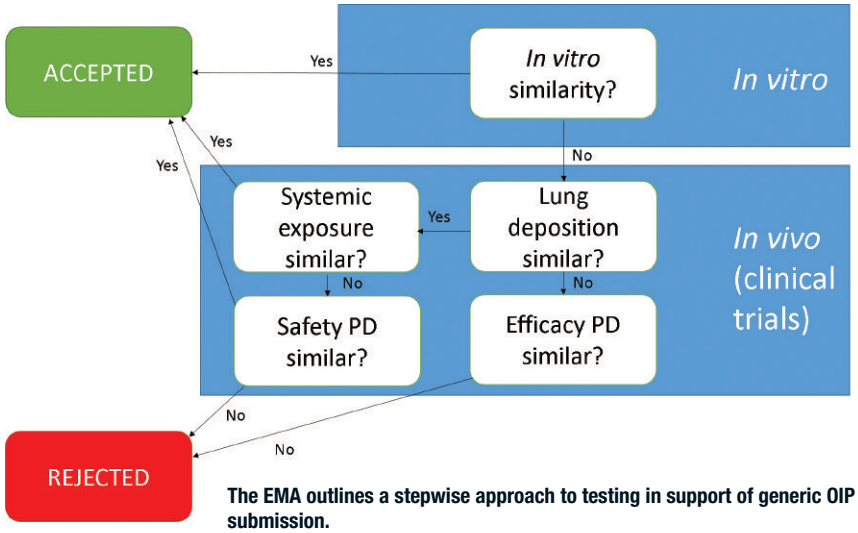
Easily repeatable and validated *in vitro* methods are relied upon for product QC. However, few good examples of IVIVCs exist for OIPs, due to factors such as variability in anatomy/impairment of the lung, device use, and compliance, which make it difficult to secure robust relationships between product characteristics and clinical efficacy. As a result, *in vitro* testing is often and necessarily supported by *in vivo* studies (PK/PD) for the demonstration of BE.

PK studies determine the fate of the drug substance within the body, primarily by tracking drug concentration in the blood plasma. PK studies are relatively straightforward to implement and can exhibit high discriminating power, particularly if a healthy patient population is used.[3] It is generally accepted that if the systemic concentration measured for T is the same or less than that measured for R then systemic effects will be equivalent or less severe. This conclusion can mitigate the need for PD testing.[3]

The use of PK studies as an indicator of pulmonary bioavailability and hence, clinical efficacy, is more challenging because it can be argued that drug concentration in the blood is the result of pulmonary fate, rather than a reliable indicator of concentration/effect at the site of action in the lung.[3-5] The implications for clinical efficacy of a difference in PK study results may therefore only be resolved via further *in vivo* studies.

PD studies quantify the biological and physiological impact of the drug substance and can be used to investigate both safety and efficacy with a high degree of clinical relevance. However, they can be relatively difficult to implement with a tendency to exhibit high variability and sensitivity. Successful implementation relies on the identification of a measurable, clinically relevant biomarker linked with the pharmacological mechanism of the drug. This biomarker must enable the demonstration of

FIGURE 2



The EMA outlines a stepwise approach to testing in support of generic OIP submission.

a dose-response relationship, when tested with representative doses, for a study to be differentiating. If T and R products result in a similar clinical endpoint, then this can only be indicative of similar efficacy if a change in dose is rigorously associated with a measurable response.[4,5]

THE REGULATORY LANDSCAPE FOR GENERIC OIPS

The complexities of PK/PD studies for OIPs, and the difficulty of establishing optimal strategies for their application in the demonstration of BE, are arguably reflected in the differences in approach in regulatory guidance in this area from the EMA and the FDA.

The stepwise approach for a generic OIP submission set out in the latest regulatory guidance released by the EMA indicates that a submission can be accepted on the basis of *in vitro* data alone (Figure 2) with no additional requirement for PK/PD testing.[6]

The elimination of PK/PD testing substantially streamlines the submission process and is highly appealing from the perspective of time and cost savings; however, few products have yet to be approved on the basis of *in vitro* test data alone. The criteria for demonstrating *in vitro* only BE are demanding and call for the test product to match not only the chemical and formulation characteristics of the reference product, but also for the devices and their behavioral characteristics to be highly similar. This can be severely limiting in practice, especially when commercial and intellectual property considerations are taken into account. Furthermore, the application of a battery of *in vitro* methods with the rigorous comparison of APSD measurements is a core element of such studies.[6,7]

The FDA has no comparable formalized guidance; however, the FDA 505(j) and 505(b)(2) pathways for generic and supergeneric OIP submissions, respectively, call for a quite different "weight of evidence" approach (Figure 3). This involves qualitative and quantitative formulation sameness, device similarity, PK (comparative systemic exposure studies) and PD studies, in addition to *in vitro* tests. Beyond this general guidance, the FDA also offers a steadily increasing number of product specific guidances for popular generic targets.[8] These too typically indicate a requirement for both *in vitro* and *in vivo* (PK/PD) testing.

This current regulatory position is that most approved generic OIPs have been subjected to some form of *in vivo* testing. Such PK/PD studies not only add in time and cost but may also introduce additional risk, with poor IVIVC data complicating the demonstration of BE. Improving the clinical relevance of *in vitro* methods to access better IVIVCs and enable the greater reliance on *in vitro* methods for BE testing is an important goal for the industry.

MOVING TOWARDS BETTER IVIVCS

New models should be selected on the basis of their ability to reflect *in vivo* predictability – the primary aim – rather than anatomical correctness, where there is a choice to be made between the two.[9] Ease of use and of production should also be considered. Simplifying models as far as possible without compromising predictability helps to realise this goal. Adopting these strategies has already resulted in the development of a number of products that can be used to improve IVIVCs, including:

- A more realistic throat model
- More representative breathing profiles
- The use of face models when testing add-on devices with face masks.
- Dissolution testing

In a standard set-up for measuring the APSD of an OIP by cascade impaction

"Easily repeatable and validated *in vitro* methods are relied upon for product QC. However, few good examples of IVIVCs exist for OIPs, due to factors such as variability in anatomy/impairment of the lung, device use, and compliance, which make it difficult to secure robust relationships between product characteristics and clinical efficacy. As a result, *in vitro* testing is often and necessarily supported by *in vivo* studies (PK/PD) for the demonstration of BE."

(Figure 4), the product is interfaced to the impactor via the standard USP/Ph.Eur. induction port. This accessory has a simple right-angled geometry allowing reproducible drug recovery. However, it has been shown to capture less of the dose delivered by an OIP than would be deposited in the mouth-throat region during routine clinical use.[10,11]

From the perspective of anatomical representativeness, the use of throat cast is a solution to this issue. However, throat casts are patient specific, difficult to manufacture reproducibly, problematic to interface with the device/impactor, and have poor durability. The Alberta Idealised Throat (AIT) on the other hand is an alternative induction port (Figure 4) with a standard, idealized geometry developed from CT patient scans.

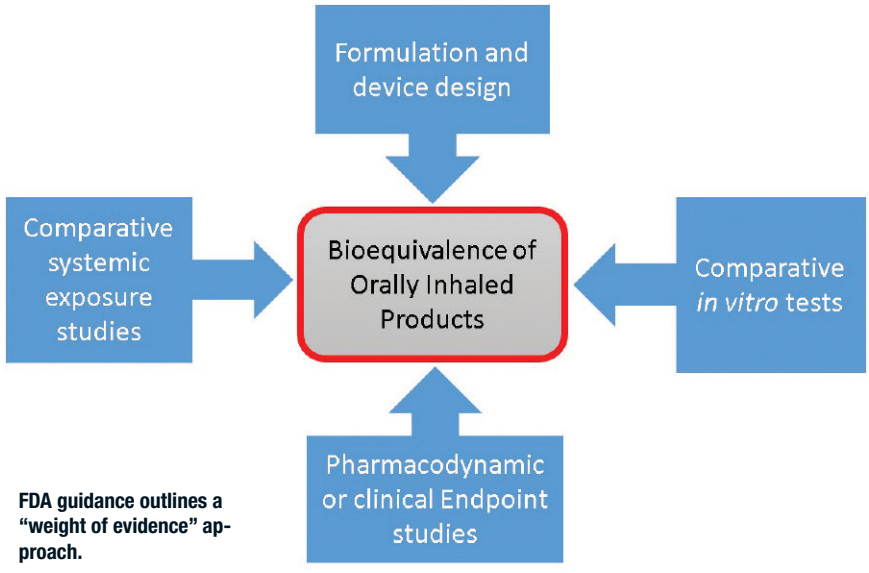
The AIT can be fully opened for drug recovery and to coat the internal surfaces to more closely simulate *in vivo* deposition. Adult and child versions are available for representative testing for specific patient groups. The AIT has been validated against clinical data over a period of around 10 years, and experimental data shows that it more accurately quantifies deposition than the standard USP/Ph.Eur. induction port.[12] This accessory is therefore a good example of a practical design that delivers enhanced predictability.

More Representative Breathing Profiles

With many OIPs, the breathing maneuver of the patient directly influences drug delivery. These include dry powder inhalers (DPIs), where aerosol generation is typically driven solely by the inhalation maneuver of the patient, and nebulizers and MDIs with spacers/valved holding chambers (VHCs), which are operated with a tidal breathing pattern. Changes to the pharmacopoeial test methods for nebulizers, and more recently for MDIs with spacers/VHCs, reflect this with defined breathing profiles now specified to simulate product use by certain patient groups.[13,14]

Breath simulators are a cost-efficient solution for investigating how breath profiles impact drug delivery performance, with commercially available systems offering the flexibility to vary defining characteristics, such as inhalation or tidal volume, inhalation/exhalation ratio, frequency, and waveforms. Such studies help to elucidate the clinical efficacy that may be observed in different patient groups and are very much aligned with a Quality by De-

FIGURE 3



FDA guidance outlines a "weight of evidence" approach.

FIGURE 4

Use of an Alberta Idealized Throat (AIT) (right) more accurately reflects the amount of drug captured in the throat than a standard USP/Ph.Eur. induction port (left).

sign (QbD) approach to product development and demonstration of BE. Indeed, confirming similarity between the performance of a T and R DPI across a range of flow rates supports claims that the products can be used interchangeably by all patients.

The Use of Face Models When Testing Add-On Devices With Face Masks

The correct use of MDIs requires the patient to begin to inhale immediately prior to actuation, thereby drawing the aerosolized dose directly into the lungs on the incoming breath. Certain patient groups, such as pediatrics, can find this level of coordination difficult to achieve and as a result, tend to use MDIs with spacers and VHCs. These inexpensive and easily retrofitted devices eliminate the need for coordination by providing a dead volume into which the dose is aerosolized, and from which the patient inhales the drug, by breathing tidally. However, the introduction of dead volume can impact both the amount and APSD of the delivered dose.

Newly released USP Chapter <1602> represents the latest thinking regarding the testing of MDIs with add-on devices and details test methods that are highly relevant for the robust demonstration of BE for MDIs.[13] In cases where the spacer or VHC features a facemask, interfacing it with the test apparatus presents a significant challenge. The chapter allows for the use of face models that have the following clinical relevant characteristics:

- Appropriate facial dimensions for the intended user age range
- Ability to apply the facemask with the predicted amount of dead space when it is applied with a clinically relevant force to the model
- Physiological accurate soft facial tissue modelling around the chin, cheeks, and nose where the facemask makes contact
- Means of correctly mounting the spacer/VHC so that the facemask is oriented with the correct alignment to the face, as would occur when in use by the patient.

Dissolution Testing

There are as yet no pharmacopoeial requirements for dissolution testing for OIPs, though this is clearly the subject of FDA interest.[15] Where inhaled particles are very small then dissolution may be extremely rapid, however, for poorly soluble drugs, dissolution testing potentially has value for achieving a better understanding of *in vivo* behavior but remains challenging due to the limited amount and varying composition of fluid in the lung.

A number of methods have been proposed for dissolution testing, including the McConville/Copley methodology, which uses existing USP/Ph. Eur. tablet dissolution testing apparatus with sample captured using an NGI with modified cup and membrane holder (an alternative insert for the Andersen Cascade Impactor is also available).[16] This set-up allows particles to be collected at defined impaction stages such that specific fractions of the APSD can be used for dissolution testing.

There is evidence that dissolution testing can distinguish between formulations of the same drug, and it is a particularly promising tool for investigating the performance of modified-release formulations, or poorly soluble drugs. However, there remain practical challenges to overcome in the development and application of suitable methodologies, not least in order to gather data that can be clearly correlated with *in vivo* behavior and clinical efficacy and that can consequently demonstrate of BE.

CONCLUSION

Demonstrating BE in OIPs requires a balance of simplicity, practicality, and reproducibility with clinical relevance. This is evident in issues associated with PK and PD studies and in moves to develop *in vitro* methods so as to improve their correlation with *in vivo* behavior. Improving clinical relevance often involves the introduction of complexity and increased variability. Greater variability translates into lower differentiating power, so a test that may be more clinically relevant for the demonstration of BE may be less able to detect a difference between a T and R product.

In vitro tests are the simplest of those to demonstrate BE, and their rigorous development toward better IVIVCs can help streamline generic OIP submissions. Optimizing the application of *in vitro* methods will help to cut the time and cost of generic development while at the same time ensuring the safety and efficacy of new products. ◆

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BIOGRAPHIES

Mark Copley graduated from the University of Bath, UK, in 2000 with a Masters in Aerospace Engineering. For 8 years, he was Technical Sales Manager and Product Specialist for Copley Scientific's range of inhaler testing equipment, before becoming the Sales Director in 2009. He is now Chief Executive Officer for the company. He is considered a leading authority in testing methods and systems for metered-dose inhalers, dry powder inhalers, nebulizers, and nasal sprays; authoring and contributing to more than 50 published articles. He also provides application support and consultancy, runs focused training workshops for the inhaled drug testing sector of the pharmaceutical industry, and sits on the editorial advisory panel of Inhalation Magazine. An invited member of the European Pharmaceutical Aerosol Group (EPAG) impactor subteam, he has also made recommendations to the Inhalanda working group, leading to subsequent revisions to Ph. Eur. and USP monographs. As part of Copley Scientific's associate membership of the International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS), he participates in a number of working groups with a view to enhancing the regulatory science of orally inhaled and nasal drug products (OINDPs).

Anna Sipitanou earned her BSc in Chemistry from the University of Bradford in 2014, and her MSc in Drug Discovery and Pharmaceutical Science from the University of Nottingham in 2015. She also undertook the role of Research Associate at the University of Nottingham, working to build in silico models for the prediction of drug induced liver injury. Building on previous experience at Cellomatics Biosciences, she joined Copley Scientific in July 2017 as Business Development Manager, playing a key role in the company's service to customers, including training on a wide range of instruments.

Special Feature

Challenging Molecules Drive Developers to Get More Creative with Excipients

By: Cindy H. Dubin, Contributor

The pharmaceutical excipients market was valued at $6 billion in 2017 and is expected to reach $8.5 billion by 2023. The growing pharmaceutical market along with advancements in functional excipients, growing generics market, and the rapidly growing biopharmaceuticals sector are the major factors driving the growth of the market. Factors such as the emergence of multifunctional and co-processed excipients, and the growing biologics and biosimilars industry also present significant opportunities for the growth of excipients.[1]

An increasing percentage of drug candidates are Developability Classification System (DCS) Class II or IV, so these molecules have solubility and/or permeability challenges that stand in the way of achieving good oral bioavailability *in vivo*. One of the most common techniques used to overcome solubility limitations is through formulating with excipients. "So as not to introduce additional approval challenges and expedite development, much of the time we first evaluate excipients that have been used in approved drug products," says Dr. Benoit Hilbold, Product Development Supervisor, Catalent. "But there are areas and situations however where current excipients fall short, such as in abuse-resistant formulations or for modified-release applications."

Thus, interest in polymers is on the rise. "A growing share of the new APIs formulated as oral dosage forms have challenging absorption properties, including low permeability, and at times, poor water solubility," says Dr. Firouz Asgarzadeh, Director Formulation and Application Services, Evonik Health Care. "These formulations often require the use of new types of excipients and polymers with advanced functionalities."

As the interest in polymers/excipients and the formulation technologies continue to rise, so does the interest in new and innovative excipients/solubilizers for achieving the desired solubility and bioavailability. Thus, the industry is taking aim at finding excipients with excellent solubilizing properties. "Excipients with amphiphilic characteristics with appropriate lipophilicity and hydrophilicity will enable the encapsulation of drugs in polymeric matrices or micellar structures to efficiently deliver the molecules with enhanced efficacy while reducing adverse effects," says Shaukat Ali, PhD, Technical Support Manager, North America, BASF Pharma Solutions.

In addition, the demand for functional polymeric excipients has increased exponentially contributing to the observed growth in the overall excipients market. Numerous commercial drug products exist because functional excipients in the formulation afford delivery of actives to the best site of absorption in the gastrointestinal tract (GIT). "Technologies and techniques developed over the past 20 years have opened up new applications for functional excipients," says Dr. Asgarzadeh. "Some examples include solid solutions and solid dispersions, multi-particulate coating systems containing permeation enhancers, enzyme inhibitors, and/or cell penetrating peptides."

This annual *Drug Development & Delivery* report highlights the technologies various excipient manufacturers are using to develop more innovative and effective ingredients to improve the performance of drug molecules.

Evonik's formulation technologies provide new approaches to targeted drug delivery.

Ashland: Improving Upon Established Excipients

Ashland is a global leader in excipients for advanced formulation of oral solid dosage forms. Typically, its excipients have been used infrequently for formulation of biologicals, but the company does supply purified (endotoxin controlled) products for niche applications and development purposes, e.g., cyclodextrins for protein stabilization, vinyl pyrrolidones for cell culture yield improvement, and sodium carboxymethylcellulose for stability of injectable formulations. However, in response to significant demands for enabling excipients for biologics, Ashland has started to explore technical development, external technology acquisition, and mergers and acquisitions.

Although pharmaceutical companies prefer to use compendial excipients with a long and proven history in the market, Ashland modifies existing excipient grades within the approved pharmacopeial boundaries. "As an example, the manufacturing of modified-release matrix tablets needs excipients with improved flow properties that maintain a robust release profile and adequate tablet properties," says Dr. Christian Muehlenfeld, Technical Leader, Pharmaceutical Research and Development, Europe, Ashland. "Therefore, Ashland diversified the Benecel hypromellose (HPMC) portfolio to offer specific grades for different modified-release applications, including Benecel DC, CR, and XR grades of HPMC."

Another example is the development of excipient grades suitable for specific processes, such as hot-melt extrusion or 3D printing. Those technologies use excipients that have been around for many years, however those processes dictate specific physical and chemical properties for excipients, explains Dr. Muehlenfeld. "At Ashland, we have improved the chemistry of copovidone and hypromellose acetate succinate to tailor excipient grades for those innovative technologies."

Ashland has a broad portfolio of excipients for oral solid dosage forms.

Ashland not only provides a broad portfolio of functional pharmaceutical excipients, but also offers technical support to customers. Such support includes helping customers to understand the impact of excipients on the quality attributes of pharmaceutical products and providing technical solutions for formulation, process development, and troubleshooting. "As a recent example, the Ashland team successfully developed a bioavailability enhanced, high drug-load product for a customer as a single tablet via HME technology using Aquasolve™ HPMCAS as the primary excipient," says Dr. Vivian Bi, Director, Pharmaceutical Technology, Ashland. "In another case, we used our STYL'One compaction simulator to help a customer predict a tablet-sticking issue during commercial-scale tablet manufacturing, which significantly reduced the formulation and process development time for our customer."

BASF Pharma Solutions: Solving the Challenges of Innovative Drug Molecules

The pharma industry is at a crossroads in the development of novel and sophisticated excipients that address solubility and bioavailability issues. Demand for such excipients continues to be high because new chemical entities are poorly soluble and less bioavailable. Other challenges include taste-masking of bitter drugs and the regulatory constraints of using novel excipients to overcome this – especially in development of pediatric formulations. As the number of molecules with challenging properties continue to rise, so are the demands for novel excipients to address unmet needs.

As the interests in novel excipients continue to rise in the industry, excipient manufacturers and pharmaceutical firms are working more closely to find the solutions that mitigate any regulatory challenges stemming either from the first-time use of an excipient in a drug. It is of more relevance in biologics as excipients are used as processing aids upstream in cell cultures for API production. Thus, highly pure excipients with minimal impurities and

"The use of excipients to increase biologic manufacturing yields and production efficiencies holds tremendous business potential in terms of reducing production costs." — Dr. Ronak Savla, Scientific Affairs Manager, Catalent.

known safety profiles have been preferred in biologics. Impurities, if not controlled, can lead to lower yield of APIs in the upstream process. BASF's Kolliphor® P188 BIO is an example of a highly purified poloxamer 188, which has been manufactured under a controlled process to minimize the impurities for improved API yield in the upstream manufacturing process.

BASF has fostered partnerships with excipient users to develop solutions to the challenges of innovative drug molecules. Examples include polymeric excipients such as Soluplus®, a graft amphiphilic copolymer with significantly large lipophilicity characteristics, having the capabilities to form complexes through hydrogen bonding and apolar or hydrophobic interactions with APIs and encapsulate them into the micellar cores, says Shaukat Ali, PhD, Technical Support Manager, North America, BASF Pharma Solutions. "Such interactions are critical to increasing solvation, hence, the solubility and maintaining the supersaturation of drugs in aqueous solutions."

Kollidon® VA 64 (Polyvinylpyrrolidone-vinyl acetate copolymer) is another example of a novel excipient that has shown to significantly increase solubility and bioavailability of a known tyrosine kinase inhibitor, he says. "These polymers also tolerate conventional and non-conventional formulation technologies that have robust processing conditions such as high shear and temperature. As the industry continues to overcome the challenges with taste-masking, BASF's novel excipients like Kollicoat® Smartseal, continue to gain attention of drug manufacturers because of its unique chemistry and physico-chemical attributes that deliver excellent taste-masking and moisture protection abilities."

Most of the excipients in BASF's portfolio are multi-functional, meaning that one excipient brings different functional characteristics depending on the application. For instance, Kollidon VA64, a dry binder and a film former for coating and acts as a good solubilizer in melt extrusion. "Kollidon VA64 and/or Kollidon VA64 Fine offer unique benefits to crystalline, poorly compressible or soluble APIs," says Dr. Ali.

Kollicoat® IR, a graft copolymer comprised of polyethylene glycol and polyvinyl alcohol), is highly flexible without any plasticizer for instant-release coating, but is also used as a peroxide-free binder for APIs highly sensitive to peroxide degradation. Kollicoat Protect, on the other hand, which is a co-processed excipient comprised of Kollicoat IR and polyvinyl alcohol, is a multi-functional excipient, used as a moisture barrier coating and directly compressible binder for development of floating or gastroretentive tablets due to its inherent porosity, low bulk density, good flowability, and high compressibility. Other examples include, Kollidon SR, which is a co-processed excipient used for controlled-release matrix tablets, while other directly compressible excipients such as lactose-based Ludipress® and mannitol-based Ludiflash® have been used as a dry binder and orally disintegrating tablets, respectively.

Catalent: Investigating the Use of Excipients to Achieve Specific Characteristics

Excipients are no longer used just to bulk up a formulation or mask taste. Functional excipients are of great interest, and where excipients were once restricted to materials with inert properties, pharmaceutical companies and their development partners are now more frequently seeking excipients that add value by improving a product's profile. Excipients are, therefore, often critical to overcoming the physicochemical and biological barriers to achieving optimal drug exposure. Improving solubility is the most common purpose for functional excipients. Lipid-based drug delivery systems are complex formulations consisting of mixtures of excipients that deliver insoluble drugs to the gastrointestinal tract in a solubilized form. Polymers used in hot-melt extrusion and spray dried dispersions keep drug molecules in an amorphous state, retard crystallization, and thus, enhance solubility.

"In addition to enhancing solubility, sophisticated or functional excipients can be used to help modulate release of drugs, improve processing and manufacturing, and improve stability," says Dr. Benoit Hilbold, Product Development Supervisor, Catalent. "Catalent has employed excipients to help in the opening of tight junctions for oral delivery of macromolecules. Catalent has investigated the use of more pure excipients to capitalize on certain properties." An excipient can be "purer" in several different ways: elimination of degradants, altering molecular ratios in

heterogenous excipients to exploit certain characteristics, and altering peroxide values. For example, Catalent has formulated softgel products that have oxygen permeability, providing greater stability for certain APIs or nutritional supplements such as cod liver oil.

An increasing percentage of the pharmaceutical pipeline is composed of biologic molecules. To reach their full commercial and therapeutic potential, these biologic molecules need to be properly formulated into drug products. "The use of excipients to increase biologic manufacturing yields and production efficiencies holds tremendous business potential in terms of reducing production costs," says Dr. Ronak Savla, Scientific Affairs Manager, Catalent. Novel excipients can reduce the time and cost associated with manufacture, not only so that patients receive the best medicines possible, but also to help companies ensure they are able to provide a reliable supply to patients.

In addition to preventing instability and aggregation during processing or storage, excipients are being sought to manufacture high concentration protein formulations. Nearly half of biologic molecules in the pipeline require a dose of 100mg or more. Such doses can't be administered using subcutaneous injections, which is preferred for outpatient treatment with biologic drugs. "Novel excipients that enable highly concentrated biologic drugs have the potential to create more patient-friendly drug products," says Dr. Savla.

Evonik Health Care: Polymer Portfolio Addresses a Range of Formulations

Formulators can realize versatile formulation and drug delivery options by leveraging the broad potential of functional polymer excipients. Evonik's portfolio of oral dosage functional polymers (EUDRAGIT®) for the past six decades, and bioresorbable polymers for parenteral drugs (RESOMER®) for the past four decades, are advanced excipients for targeted or modified drug delivery, says Dr. Firouz Asgarzadeh, Director Formulation and Application Services, Evonik Health Care.

Specific drug release characteristics can also be achieved by combining different excipients, such as a time-controlled permeable yet insoluble polymer with inorganic or organic salts. Advancements in co-processed excipients can bring unique advantages to the excipients market. Evonik added co-processed excipients to its polymer portfolio, such as EUDRAGIT E PO ReadyMix for fully formulated taste masking and moisture protection with custom color-matching services, and PlasACRYL® an easy-to-use excipient suspension containing plasticizer and glidant. "These excipients provide significant time and cost savings in production plus the added benefit of higher formulation safety," says Dr. Asgarzadeh.

Evonik has also developed alcohol-resistant coatings for multi-particulates using EUDRAGIT polymers combined with sodium alginate. "These formulation solutions are popular because there are no regulatory hurdles to overcome as with new excipients," says Dr. Asgarzadeh. "In our experience, most pharmaceutical companies prefer these easier approaches because they reduce development efforts and time to market." Developing new excipients with specific properties will be considered for drugs with a high market potential and if none of the commercially available excipient solutions yields the desired results. In some cases, intellectual property can play a role in new excipient design decisions. This is especially true for parenteral depot formulations. To this end, Evonik launched RESOMER® Select bioresorbable polymers.

"Overall, our aim is to ensure that newly developed drug delivery excipients are compendial according to the major pharmacopeias," says Dr. Asgarzadeh. As an example, in 2017, Evonik launched EUDRAGIT FS 100 powder, which allows pharmaceutical companies to use this well-known polymer in new applications like hot-melt extrusion, solvent spray drying, and solvent coatings.

Gattefossé: Fine Tuning Existing Excipients

Given the enormous costs of developing raw materials, need to characterize safety profiles, and the tortuous regulatory pathway one travels for their approval, developing novel excipients is not a straightforward option. Instead of embracing the new or the unknown, the pharmaceutical industry can also rely on innovation with existing and well-characterized materials.

Working within established excipients' safety and regulatory constraints, Gattefossé is focused on fine tuning and refining currently monographed excipients to develop products with specific functionalities, such as enhancing bioavailability, solubility, permeation, and/or modifying drug release rate for use in different processing techniques.

"We have focused on process and formulation technologies to expand the scope of innovation with excipients," says Ron Permutt, Senior Director-Pharmaceutical Division, Gattefossé USA. "Polyoxylglycerides like Gelucire® 44/14, 50/13, and 48/16 are perfect examples of such developments. Differing in fatty acid compositions, melting points, and hydrophilicities, these excipients offer a range of solubility

Gattefossé excipients are functional and safe for pediatric formulations.

and bioavailability enhancement properties when used in melt granulation, capsule filling, tableting, and melt extrusion systems."

Additionally, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), and self nano-emulsifying drug delivery systems (SEDDS) have been successfully applied in the delivery of various types of poorly soluble molecules, including biologics. Articles published by Gattefossé scientists discuss recent advancements in SEDDS formulations for protein delivery. "The work involves successful conversion of water-soluble peptides to oil-soluble peptides via hydrophobic ion pairing (HIP), and their incorporation into SEDDS formulations," says Mr. Permutt. "The results demonstrate the utility of the approach in protecting the peptides from degradative conditions afforded by formulation of the HIP-peptides."

Solubility and bioavailability can be enhanced in SLN/NLC with the multi-functional excipient, Compritol® 888 ATO, explains Mr. Permutt. Defined as atomized glyceryl dibehenate, Compritol may be used up to 3% w/w in direct compression for its superior lubricant properties and at 15-30% w/w as sustained release matrix former. In melt congealing and melt extrusion processes, it is used for modified release. "An important property of this excipient is its superior safety profile and mild taste making it suitable for pediatric dosage forms," he says.

In 2017, Gattefossé launched the Gattefossé Technical Center of Excellence (TCE), which supports customer projects. Services include solubility screening and formulation design and development. In addition, *in vitro* lipolysis testing is offered to assess the impact of *in vivo* digestion and its potential effect on the *in vivo* performance of lipid formulations. "Through the use of these services, customers have reduced the amount of time ordinarily needed to develop workable drug formulations," says Mr. Permutt.

LONZA Pharma & Biotech: HPMC-Based Capsules Offer Enteric Properties Without Additional Coatings

Drug discovery is shifting toward complex and life-threatening diseases, often requiring more sophisticated drug delivery technologies to achieve the therapeutic outcomes. Appropriate selection of excipients and excipient combinations can provide a therapeutic benefit, such as facilitating drug absorption or protecting the active ingredient from degradation. Moreover, it can reduce the overall complexity of a formulation or manufacturing process. For example, two-piece capsules are an excipient that is used for oral and inhalation drug therapy. The capsules provide different functionality based on the shell composition and manufacture.

With the development of HPMC capsules manufactured by a thermogelation process, drug absorption can be significantly enhanced due to the crystallization inhibiting effect of HPMC in solution.2 "HPMC-based capsules such as Vcaps® Plus, are very inert against low moisture or higher temperatures, which specifically addresses the needs of emerging markets to enable cost-effective and regional manufacturing across the globe," says Sven Stegemann, PhD, Director of Pharmaceutical Business Development, Lonza Pharma & Biotech.

LONZA Pharma & Biotech offers a broad portfolio of HPMC-AS- and HPMC-based capsules using the thermogelation process. These capsules provide enteric properties without any additional coating or sealing process. This is especially useful for compounds that should be released in the intestine, but which are sensitive to compression.

LONZA Pharma & Biotech, pioneered enTRinsic™ drug delivery technology to provide oral delivery with full enteric protection and rapid release (at pH 5.5) in the upper GI tract without the use of coatings. EnTRinsic capsules are manufactured using pharmaceutical grades of cellulosic enteric derivatives.

Hassan Benameur, Senior Director, Pharmaceutical Sciences, Lonza Pharma & Biotech says that enTRinsic drug delivery technology is applicable to a range of sensitive molecules including nucleotides, peptides, vaccines, and live biotherapeutic products. Independent analysis estimates time savings afforded by enTRinsic drug delivery technology of 9 months or more through Phase III.

"Functional excipients and advanced processing will continue to be an essential part of innovation in drug delivery," says Dr. Stegemann. "The closer integration of the drug synthesis into the drug delivery development and manufacturing will even increase the space for innovative solutions to address the various challenges of the future of healthcare delivery."

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BIOGRAPHY

Cindy H. Dubin is an award-winning journalist who has been reporting on the pharmaceutical industry for more than 17 years about a variety of topics, including formulation development, drug delivery, and drug quality.

FDA UPDATE

The FDA's New Drug Approval Process: Development & Premarket Applications

By: Kaiser J. Aziz, PhD

INTRODUCTION

The Food and Drug Administration (FDA) is responsible for advancing the public health by helping to speed innovations that make medicines safer and more effective and by helping the public get the accurate, science-based information it needs to use medicines to maintain and improve public health. This publication emphasizes quality system approaches to the development and availability of new drug information presented in the proposed labeling of the product. In 2004, the FDA provided a guidance document for innovations, challenges, and solutions for new drug products that examine the critical path needed to bring therapeutic products to completion, and how the FDA can collaborate in the process, from laboratory to production to end use, to make medical breakthroughs available to those in need as quickly as possible.

DRUG DEVELOPMENT RESEARCH

One of the primary functions of a firm's research project team is to coordinate the various studies necessary for the successful development of a drug candidate and to plan a timeline for developmental activities for its premarket application. This coordination is usually accomplished by preparing a detailed drug development plan and monitoring the research process. This requires analyzing the information and studies as they relate to the proposed drug candidate type commonly referred to as a novel chemical entity for disease indication and the intended use (ie, cardiovascular, cancer, CNS indications, diabetes, etc). This includes types and duration of therapies (ie, acute or chronic situations with one or a few doses adequate for treatment modes). It's also important to consider routes of administration (ie, intravenous or infusion or nonintravenous such as oral, pulmonary, subcutaneous, intramuscular, dermal, etc). The timelines for the various studies and their integration into a formal drug development plan are compound-specific and dependent on the availability of resources within the various departments of the sponsor firm and approval of CROs. At the same time, the designation of pertinent milestone events and the critical path are compound-specific and firm-specific. Additionally, studies, such as bioavailability for a candidate drug may be necessary. Other studies, such as potency, immunogenicity, and toxicity may be required. The formation of various project teams requires coordination for the successful development of a drug candidate for premarket applications submitted to the FDA.

STUDY DESIGN

The research teams should carefully review and evaluate the prototype design studies for the candidate drug as to how it is similar or different from the intended clinical use and determine whether the appropriate subject population and resources are available at a given institution and whether any requirements unique to the protocol can be met at that site. In addition to identifying the type of study, the team should consider as to how the protocol requirements compare to the routine standard of care for the selected patient population. The team should consider as to how the drug dosing will be determined.

PRECLINICAL DRUG DEVELOPMENT

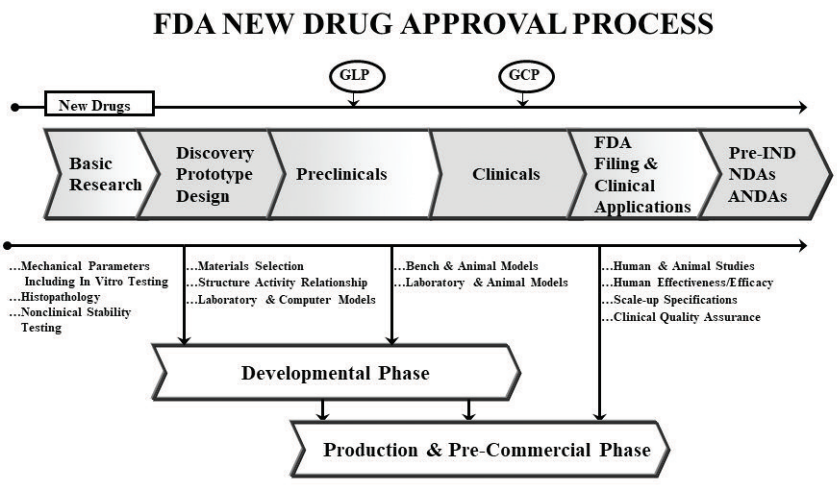
The drug candidate is subjected to a number of preclinical studies to establish and characterize its safety profile. New drugs must be shown to be safe and effective in human subjects before FDA approval. The drug company must first convince the FDA that the drug is reasonably safe to use in humans to evaluate safety

and efficacy in clinical studies. This is established through preclinical laboratory testing, including testing in animals. These studies of a new compound or drug, generally performed in animals, are referred to as "preclinical studies" (Figures 1 & 2). Preclinical studies help establish boundaries for the safe use of the treatment when human testing or "clinical trials" begin. The sponsor of the new drug product submits an IND application to the FDA requesting permission to initiate clinical trials. The results from preclinical studies are documented in scientific publications or technical reports and used to prepare as part of premarket submission for the initiation of human clinical trials. The preclinical studies on a potential drug substance are required to follow Good Laboratory Practices (GLPs) regulations. GLPs govern laboratory facilities, personnel, equipment, and operations. Compliance with GLPs requires procedures and documentation of training, study schedules, processes, and status reports, which are submitted to facility management and included in the final study report to the FDA. The preclinical studies data are gathered to reach the goal of potential therapeutic effect and reasonable safety index and the drug sponsor must notify the FDA of its intent to test the potential new drug in humans. The application to request permission to begin human testing is commonly referred to as an Investigational New Drug (IND) application. The IND allows the use of an investigational drug in human subjects for the sole purpose of conducting clinical trials.

GOOD LABORATORY PRACTICE (GLP)

GLPs are the regulations for the nonclinical laboratory studies to support

FIGURE 1



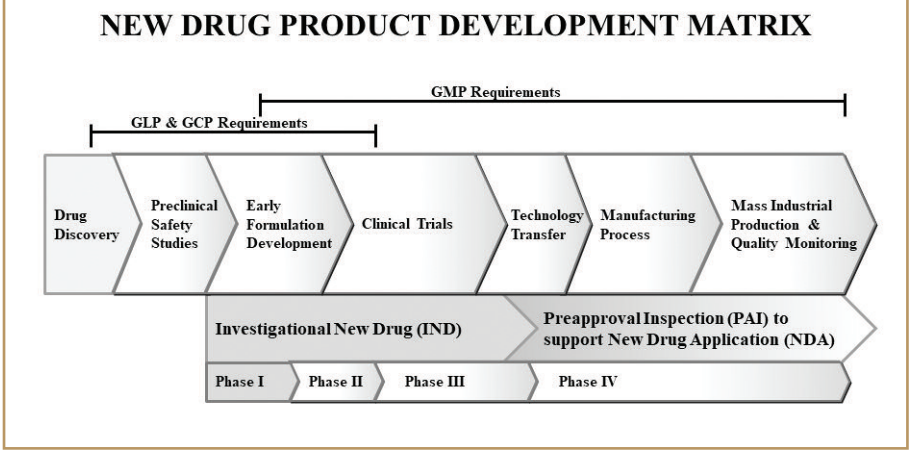
INDs). FDA regulations applicable to GLPs are provided in (21 CFR, Part 58). GLP regulations require protocols for standard methods, facilities, equipment, test controls, records and reports, audits, and inspections to be used in conducting preclinical and nonclinical laboratory studies that are used to ensure the quality and integrity of data provided in INDs. Nonclinical studies include in vitro and in vivo experiments for the new drug safety profiles. GLP standards relate to both the design and the conduct of laboratory studies and the qualifications of the personnel and facilities involved with the experiments. The purpose of GLP is to ensure the integrity of the nonclinical safety data, such that an evaluation of the study quality and inter pretation of the study results may be done with confidence. Guidance documents related to GLPs are issued by the FDA and ICH (International Conference on Harmonization) as illustrated as part of Quality System Model presented in Figure 3. The GLP highlights are:

- SOPs written for routine or standard practices in the laboratory
- Personnel involved with the studies are trained and experienced
- The facilities are appropriately designed and maintained
- A group, commonly called quality assurance or QA, monitors and checks the results from the studies to ensure that the experiments are conducted in compliance with regulations

GOOD CLINICAL PRACTICE (GCP)

FDA regulations applicable to GCPs are provided in (21 CFR 312). The FDA has published a consolidated guideline of GCP in conjunction with the ICH guideline {E6, 62 Fed. Reg. 25692 (1998)}. The consolidated guideline for GCP is intended to provide a unified standard for conducting clinical studies. These standards apply to all aspects of clinical trials, from protocol design, monitoring, and auditing, to recording, analysis, and reporting of clinical data presented in new drug applications to the FDA. Guidance documents

FIGURE 2



related to GCPs are issued by FDA and ICH as illustrated as part of Quality System Model presented in Figure 3. The overall aim of GCP is to protect public health and the rights, welfare, and confidentiality of study participants. The GCP process is intended to ensure that all data and reported results are credible, accurate, and evidence-based. While GCP places emphasis on the clinical accuracy of results, it also deals with the importance of the processes used to conduct clinical trials.[1-5] FDA is focused on the conduct of clinical trials and embracing GCPs as a "Quality System Approach to New Drug Development and Approvals"- (Figure 3). According to this approach GCP refers to the collection of regulations and requirements that must be complied with while conducting clinical trials. These regulations apply to manufacturers, sponsors, clinical investigators, and institutional review boards.[1,5]

PRINCIPLES & PROCEDURES FOR NEW DRUG APPLICATIONS

The FDA new drug approval process begins with research plans involving basic research, laboratory, and animal testing. This initial stage includes discovery and development of prototypes involving preclinical and clinical studies of new drug materials to be reviewed and approved by an institutional review board (IRB). These IRBs exist in hospitals, university medical centers, and private clinical research institutions at which clinical trials take place. Before a clinical trial is initiated, foreseeable risks are weighed against the anticipated benefits for the individual trial subject and the intended clinical population. Generally, a clinical trial is initiated and continued only if the anticipated benefits are feasible (Figure 1). The FDA filing and premarket applications consist of the following categories:

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

For a drug manufacturer to introduce a product in the market for human use, a multiphase procedure is followed. This procedure begins with a number of preclinical or "prior to human" testing, followed usually by three phases of human studies.[1,3,5] New drugs are also subject to a fourth phase, known as post-market surveillance, which may require additional trial data. The FDA has published detailed information on the drug development process (www.fda.gov/cder/handbook/develop.htm). This publication not only addresses the importance of interactions between the sponsor and the FDA, but also emphasizes the interactions between the various stages of investigational studies and the continuing dialogue with the FDA review status throughout the development and completion of premarket application.

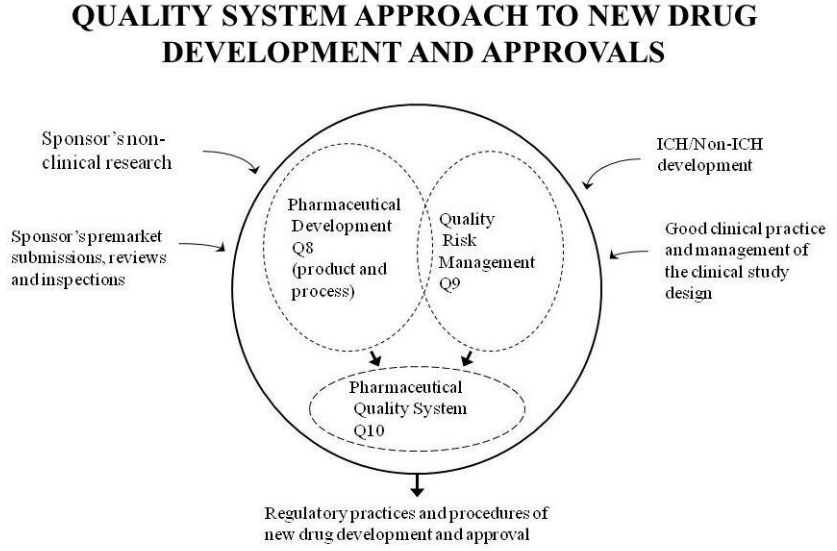
IND is a submission to the FDA requesting permission to initiate a clinical study of a new drug product in the US. The main purpose of an IND is to seek an "exemption" from the Act's prohibition of introducing any new drug into interstate commerce without an approved application, or to allow a firm to request permission to ship an "unapproved drug" or import the new drug from a foreign country. IND allows a company to initiate and conduct clinical studies of their investigational drug product. These studies are used to gather significant evidence of reasonable safety and efficacy data about the candidate drug compound in humans. Numerous meetings between the sponsor and the FDA take place during these studies The requirements for the format and content of the IND application are provided in (21 CFR Part 312).

NDA is a premarket submission to the US FDA requesting to obtain approval for marketing a new drug in the US. The FDA reviews the NDA application and ultimately makes the decision on whether the drug application is fillable (Figure 1). Prior to making the decision, the FDA will arrange for an advisory committee meeting of outside experts to seek their recommendation in regard to the approvability of the premarket application. The recommendations of an advisory committee are

not binding, but the agency considers them very carefully when making approval decisions. The NDA submission is organized into specific technical sections, which are evaluated by specialized FDA review teams. The review teams recommend approval or disapproval. The FDA authority to require an NDA (prior to marketing the drug product in the US) is drawn from section 505 of the Food, Drug and Cosmetic Act {21 USC 355}. The content and format of an NDA is laid out in 21 CFR Part 314 and guidance documents published by FDA (http://www.fda/cder/guidance/5445fnl.htm#Toc77574464). When all the aforementioned steps are completed, the FDA inspects the manufacturing plant to ensure the sponsor's facilities are capable of manufacturing the drug in compliance with the FDA's current good manufacturing practices (cGMP) regulations (Figure 2).

ANDA is for new drugs approved which must be pharmaceutically equivalent and bioequivalent to predicate product, usually an innovator or pioneer drug (reference listed product 21CFR 314.94) ANDA is a submission to FDA as an ANDA .These applications are called "abbreviated" because the generic drug manufacturers are not required to include preclinical or clinical data to establish safety and effectiveness because those characteristics were already established by the manufacturer of the innovator drug through the NDA process. The sponsor of an ANDA must provide information and data demonstrating that the drug product is bioequivalent to the innovator drug and the proposed use and labeling is identical to that of the reference innovator drug. ANDA sponsor manufacturers are subject to the same inspection requirements that apply to manufacturers of new innovator drugs.

FIGURE 3



CLINICAL TRIALS

Clinical trials are an integral part of new drug discovery and development; and they require review and evaluation by the FDA before the new drug product can be brought to market. Before submitting an NDA, the sponsor must conduct preclinical and clinical studies designed to demonstrate the safety and efficacy of the drug product. Clinical trials involve studies of human subjects where the protocol-designed studies provide information and data to support the NDA submission to FDA. Clinical trials may be classified by their stage and phase in the product life cycle and are generally categorized into three phases (Figure 2).[1-5] Clinical trials require careful planning and consideration of the types of subjects to be enrolled. The main purpose of clinical trials design objectives is to test a hypothesis and ultimately to reach a conclusion as to whether a drug product has any effect on the human body and the disease condition in which it is being tested. Additionally, the drug product improves the subject's health or quality of life, have an advantage over the current treatment available for that disease or condition, and can be administered safely to that subject. Sponsors of drug product studies are required to control risks to clinical trial participants. It is critical that all personnel involved in clinical trials understand the regulations and guidelines that govern the protection of human subjects while evaluating the efficacy of the products.

CLINICAL TRIAL PHASES

Clinical trials for new drugs typically consist of three phases. Phase I involves a relatively small number of subjects (less than 100) intended to gather initial safety information. Its purpose is to determine a safe dose range in which the drug can be administered, metabolized, and pharmacologically effective with minimum toxicity. The safety and pharmacokinetics of the doses in these studies usually include testing to help establish the relationship between drug dose and plasma concentration levels, as well as therapeutic or toxic effects. The results of the Phase I studies are used to develop Phase II.

FIGURE 4

FLOW DIAGRAM FOR GMP INSPECTIONS

Quality System Approaches:

- **Periodic management reviews of product quality**
- **Monitor quality system requirements and customer satisfaction**
- **Track complaints and service records**
- **Find quality failures and have plans for corrective and preventive actions (CAPA)**
- **Internal audits**

http://www.fda.gov/cder/guidance/4286fnl.htm

Phase II involves a large number of subjects who have the disease or condition the drug product is intended to treat (usually 100-300). The purpose of Phase II studies is to determine a minimum and maximum effective dose (dose-ranging study and pharmacokinetic data). Clear evidence is established to confirm that the mechanism of action observed in animals is observed in humans. Phase II may be divided into two subparts: Phase IIa is a pilot study, which is used to determine initial efficacy, and Phase IIb uses controlled studies on several hundred patients. Sufficient data regarding tolerability and efficacy of a number of different dose regimens should be available to support the dose regimen to be evaluated in Phase III trials. At this point, the sponsor and the FDA usually confer to discuss the data and plans for Phase III.

Phase III studies are considered "pivotal", designed to collect all of the essential data to fulfill the safety and efficacy criteria that the FDA requires to approve the new drug application for the US marketplace. Phase III studies are usually very large, consisting of thousands of patients usually in double-blind, randomized, controlled studies that are often conducted at multiple sites. In this phase, detailed data are gathered about the effectiveness of new drug compound in comparison to control treatments. Subjects are followed to evaluate side effects and safety. Additionally, Phase III studies establish effectiveness of final formulation, indications for clinical use, labeling, marketing claims, drug product stability, packaging, and storage conditions (Figures 1 & 2). Upon completion of Phase III, all clinical studies are completed and the sponsor submits an NDA to the FDA for premarket approval to market the new drug in US.

FDA'S GOOD MANUFACTURING PRACTICES (CGMPS) & PRE-APPROVAL INSPECTIONS (PAIS)

Current Good Manufacturing Practices (cGMPs)

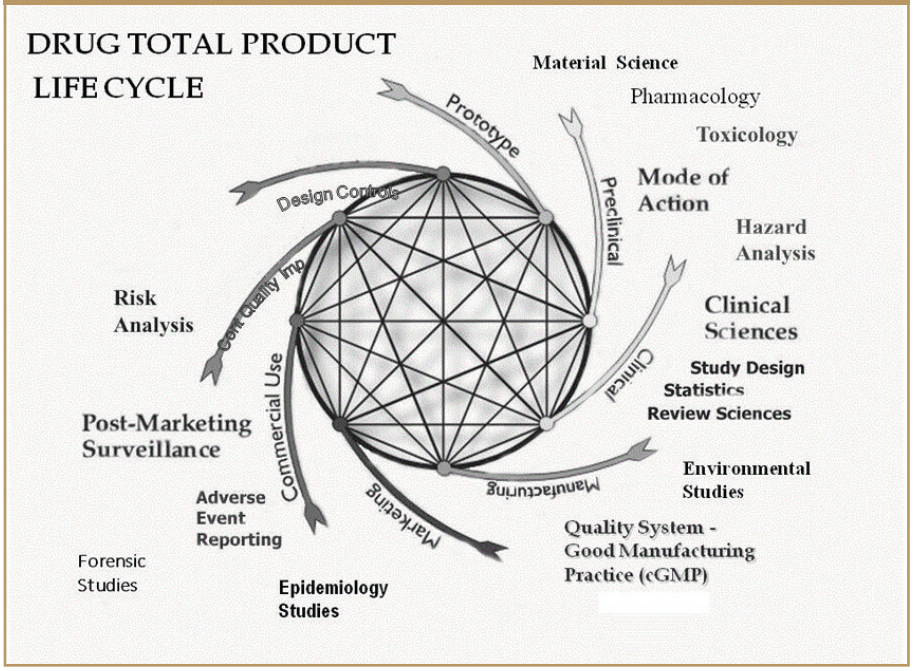
Pharmaceutical cGMPs (Title 21 CFR 210 & 211) are the part of quality assurance practices that ensure the drug products are consistently produced and controlled in conformance with quality standards (Figure 4).[1] They are known as current manufacturing practices, processing, packing, or holding of drugs and current manufacturing practices for finished pharmaceuticals. The ICH Q10 was adopted by US in 2009. The FDA guidance, "Quality Systems Approach to Pharmaceutical CGMPs" describes the aim of the agency to help manufacturers implementing modern quality systems and risk management tools to meet the requirements of the agency's current approaches to cGMPs. The implementation of ICH Q10 throughout the product life cycle facilitates and strengthens the link between drug development and manufacturing activities. In addition to ICH Q10, the FDA adopted industry sponsored guidelines for continuous quality improvement (ISBN 0273 -3099). The FDA appears committed to support ways to promote drug development, and is willing to accommodate NDA sponsors to use improved quality management approaches to foster innovations and improvements. These approaches help enhance the consistency and coordination of the FDA's drug quality regulatory programs, in part, by further integrating enhanced quality systems approaches into the agency's regulatory processes concerning review and inspection activities. In reference to NDAs, cGMPs include quality system approaches whereby the sponsor addresses the specifications of the drug product and the manufacturing process controls from the prototype design to the production and release of the finished product (Figure 4). The FDA's CGMP regulations do not prescribe in detail how a manufacturer must proceed as it designs and manufactures a specific drug product. Instead, a framework is presented requiring the manufacturer to develop and follow procedures and to fill in the appropriate details for a particular drug; however, the most important point behind GMP regulations is that quality must be designed and built into a product. As development pro-

ceeds, the active drug substance and dose form must be manufactured at larger scales. This scale-up may introduce variations in the manufacturing steps of drug product. Thus, it is critical to monitor the drug substance and product for variations during development and manufacturing processes. The emphasis of design controls drug GMPs should be on products that conform to defined user needs and intended uses. For NDA applications, it is essential to have data showing that the product and active drug substance have documented stability in the packaging that will be used for marketed product. FDA GMP regulations require information about all the steps of the manufacturing process from incoming materials to final distribution of the product (Figure 4).

Drug Product Life Cycle (DPLC)

The design phase of drug product life cycle is the most important development stage in regard to the lifecycle of the drug. It is at the design stage that the inherent safety and efficacy of a drug are established. The review and periodic management of design and processes involved in the drug product development are essential to maintain the drug quality toward completion of production specifications. Design maintenance activities during the development process ensures that design outputs are verified as suitable for manufacturing before becoming final production specifications.[2] The flow diagram for GMP inspections represents the process flow for the FDA's inspections for design control requirements. The FDA investigator verifies that the formulation, manufacturing, or processing methods are consistent with descriptions contained in the section of the NDA application. Manufacturing process flowcharts provide road maps to FDA investigators. They provide a detailed view of the process, and increase understanding of how the process flows. With a process flowchart, FDA investigator can identify critical control points of manufacturing processes.[1-3]

FIGURE 5



Hazard Analysis & Risk Assessment

The DPLC for an NDA drug product is an integrated development and marketing framework. The DPLC can be divided into the following segments:

- Early product cycle (concept, prototype)
- Mid product cycle (pre-clinical, clinical, manufacturing)
- Late product cycle (marketing, commercial use, continuous quality improvement, and design controls)

All segments of DPLC are interconnected to every other phase with the final drug product providing built-in quality and process improvement. Issues learned from one part of a life cycle are applied to the development of the next generation. The essential principles of DPLC are composed of management responsibilities, quality assurance, and drug design monitoring units (Figure 5). The ICH quality system approach requires sponsors of NDAs to establish and maintain procedures to control the design of the drug product in order to ensure that specified requirements are met. As previously mentioned, intrinsic quality of the NDA drug product including its safety and efficacy are established during the design phase. Thus, appropriate drug design controls are observed and maintained during production stages of development so that finished drug products are safe and effective for their intended clinical use and points of disposals. Process validation (PV) is a requirement of the FDA's cGMP regulation and typically, the drug industry approach to PV has been to evaluate prospective batches incorporating risk analysis in regard to complexity of the manufacturing process or dosage form, unit operations, or critical control points in developmental stages.[1]

A quality system approach to new drug development and approval starts by defining the intended use, indications for

use, drug design controls, impact of risk analysis, and any foreseeable drug errors and clinically incorrect patient diagnosis and/or treatments (ie, adverse events). The FDA's 21st century cGMP and ICH initiatives (such as Q8 Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System), evolved into new regulatory practices and procedures for NDA applications and approvals (Figures 3 & 5). Risk management can be applicable in several areas of PV, from early process/development through maintenance of validated stages during manufacturing processes.[1-5] Some of the benefits of science- and risk-based approaches during PV are as follows:

- Benefits process understanding by proactive identification of failure modes (hazards), and managing the identified risks as early on in the product life cycle
- Enables that high risk, critical aspects of the process are well recognized by appropriately designed studies
- Monitoring of risks reduces product and process failures

It is important to assess the risks in each manufacturing process steps. The assessment starts by identifying the potential risks then controlling them to an acceptable level to ensure that drug product consistently meets approved quality standards.[1] The FDA's Quality by Design (QbD) guidances provide a sound framework for design controls from product development to the commercial manufacturing processes and for post-development changes and optimization. The QbD concepts are outlined in ICH Q8, Q9, and Q10 guidelines. These ICH documents are already adopted by the FDA. The QbD approach can be maintained throughout the life cycle of the product to facilitate continuous quality improvement (CQI). In contrast, previously, traditional pharmaceutical manufacturing relied heavily on end product testing, and the process typically lacked the flexibility needed to respond to variables encountered during manufacturing processes. The application of Hazard Analysis Critical Control Points (HACCP) principles identifies critical control points (CCPs) in the manufacturing process that require control monitoring because of detection of out-of-limits or drifts when they occur.[1-5] The HACCP system provides a focus on the CCPs most likely to control product safety. This approach allows FDA reviewers and investigators to evaluate CCPs over time by examining a firm's monitoring and corrective action records. Investigators can verify the HACCP application by confirming that significant product safety hazards are properly identified and the appropriate controls are in place.

SUMMARY

New drug applications are reviewed primarily for safety and efficacy with regard to their claims for intended clinical use. The FDA's mission is to facilitate the development of the premarket review and evaluation of INDs and NDAs. A central theme over the past few years has been a standardized approach to evidence-based review and evaluation. The FDA emphasizes the Quality System approach to design of studies by providing oversight and objective review by setting thresholds for product safety and effectiveness by ensuring that organized data and appropriate labeling are present in support of the new drug's intended and clinical use. ◆

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BIOGRAPHY

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

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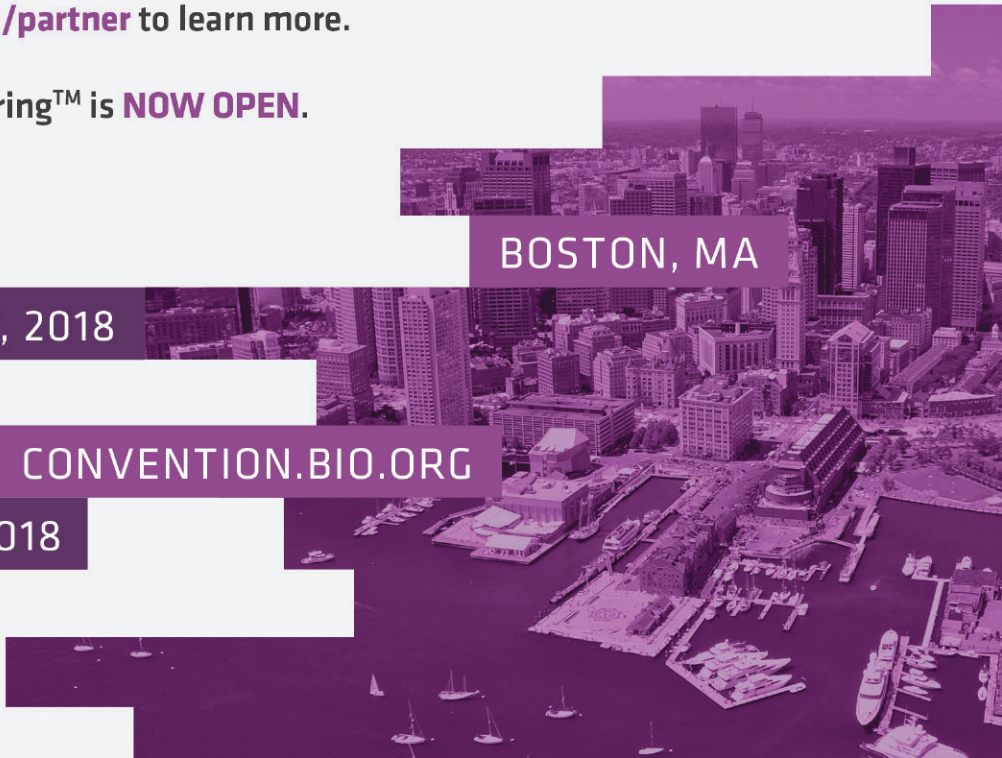

Drug Development
EXECUTIVE

Dave Backer

Head of Virus & Gene Therapy Strategic Initiatives

MilliporeSigma

MilliporeSigma: Accelerating the Development & Manufacture of Gene Therapies, Immunotherapies & Viral Vaccines

MilliporeSigma, a leader in the life science industry, works hand-in-hand with the global scientific community to develop, manufacture, and market products and solutions that bring customers one step closer to solving the toughest life science problems. With 19,000 employees and 65 manufacturing sites worldwide, MilliporeSigma has a portfolio of more than 300,000 products enabling scientific discovery. The company combines its expertise in biopharmaceutical manufacturing and high-technology products to accelerate the development of gene- and cell-based therapeutics. *Drug Development & Delivery* recently interviewed Dave Backer, Head of Virus & Gene Therapy Strategic Initiatives at MilliporeSigma, to discuss its expanding GMP capacity to speed development and manufacture of gene therapies, immunotherapies, and viral vaccines.

Q: MilliporeSigma recently expanded its GMP capacity for gene therapy, immunotherapy, and viral vaccine production by almost 90% What were the driving forces behind this expansion, and what new services/capabilities will you be offering?

A: The clinical manufacturing of intermediates and final products used in viral vaccines and gene therapies requires dedicated facilities, and there is significant demand for these services in the growing cell and gene therapy market. The Carlsbad expansion is designed to meet this growing demand. Our primary objective is to double our capacity for bulk drug manufacturing in response to customer demand. Our new suites were built with a modular design and can be used in a flexible way to meet both medium and larger scale production needs. This expansion will allow us to scale the manufacturing process for our customers as they prepare to commercialize their products.

Q: What are the biggest challenges facing development and manufacturing of gene therapies and immunotherapies?

A: One of the main challenges in this space is moving from clinical- to commercial-scale development. It's important to plan early for a scalable production platform where you understand your critical process parameters. Gene therapy, in particular, has relied on processes developed for small-scale, academic settings that were appropriate for early stage clinical trials. Often, companies are hesitant to move away from these proven technologies, and this can be a challenge when it comes to scalability. It's much more efficient to do two large production runs rather than 10 small runs, but this requires good planning, process development, characterization, and validation. Taking the time to generate sufficient data to define operating windows for critical process parameters and developing a robust, scalable process is key to commercial success.

Q: To what extent and how must manufacturing capabilities for these innovative therapies evolve in order to successfully bring them to large numbers of patients?

A: There have been a number of advances in gene therapy and gene-modified cell therapy space, particularly around the gene delivery vectors like adeno-associated virus and lentivirus that are very exciting scientifically and also leading to some very promising clinical results. But as these therapies are making their way through clinical trials and approaching commercialization, the field is beginning to realize that process engineering innovation must happen in parallel to enable commercial production to be robust, scalable, and cost effective. There are real opportunities to improve production yield as well as viral vector purity through the combination of cell line and media development, bioreactor-based expansion, and downstream processing improvements.

This is an area where we need to take the next big step forward to enable cell and gene therapy. We are certainly focused on this through the combination of our Carlsbad viral manufacturing experience and our MilliporeSigma product and process knowledge.

Q: What are some innovations that MilliporeSigma has incorporated into this facility and how are those innovations accelerating the progress of these therapies to the bedside?

A: The Carlsbad facility has been supporting the development of therapies for cancer, cardiovascular, and central nervous system disease for more than a decade. The new expansion will house twice the warehouse capacity and will incorporate both fixed- and single-use equipment in a flexible, scalable format. The expansion is necessary primarily to meet the increased demands of existing clients, but will allow for an expansion of services to new entries into the gene therapy field as well.

The Carlsbad campus features segregated fill/finish capacity for gene therapy, viral vaccine, and immunotherapy products. Our expanded capacity allows us to seamlessly support customers with a full offering from clinical to commercial scales, and is complemented by cell-banking services in Rockville, MD; viral

"There have been a number of advances in gene therapy and gene-modified cell therapy space, particularly around the gene delivery vectors like adeno-associated virus and lentivirus that are very exciting scientifically and also leading to some very promising clinical results. But as these therapies are making their way through clinical trials and approaching commercialization, the field is beginning to realize that process engineering innovation must happen in parallel to enable commercial production to be robust, scalable, and cost effective."

and gene therapy manufacturing capacity in Glasgow, Scotland; and global BioReliance® biosafety testing offering.

Q: Manufacturing gene and immunotherapies appears to be quite different from manufacturing biologics, such as monoclonal antibodies or recombinant proteins. What are some of key differences, and how are they being addressed?

A: There are certainly differences in manufacturing gene and immunotherapies as compared to more mature biologic products, such as monoclonal antibodies, but there are similarities as well. The same principles apply, and the same cGMP requirements can be applied to determine process validation and compliance of the manufacturing facilities. Most of all, manufacturers face the same production issues, such as scalability, cost efficiency, and product stability. A highly reproducible, cost-effective manufacturing process is one of the major challenges for immunotherapy manufacturing, and the same holds true for biologics. We understand that as partners of drug manufacturers, we must engage in informed conversations about the entire production flow. In fact, the use of sterile, single-use disposable materials has always been part of our manufacturing platform. And now, as the industry moves more aggressively toward cell and gene therapies, there is definitely a continuing shift toward closed, pre-sterilized manufacturing systems, and particularly toward single-use bioreactors. On the downstream side, disposable single-use and pre-packed columns are also driving efficiency. Similar to our expansion, the move toward modular, single-use- based facilities is making manufacturing more flexible and able to be tailored to a drug product's manufacturing needs.

As to differences, we have to treat each viral product as potentially infectious, even when they are fully attenuated. That requires specific facility designs, standard operating procedures, and dedicated areas in which to manufacture these products. Viral products also have wide variability in productivity, vector stability, and size. Thus, the site has developed a robust set of capabilities for these products, and we need to keep those skill sets while also scaling up and validating processes for commercialization. For cell therapy production, which our customers perform, but we do not perform at Carlsbad, autologous or personalized therapies are scaled out, while allogeniec, or off-the- shelf, therapies are scaled up. Scaling up and scaling out are quite different. When scaling out, you need good scale down models that can predict performance at a larger scale. You want to do the bulk of your process development at small scale to be economical and practical. However, you need confidence that the same process parameters will lead to the same product at large scale, with the same quality characteristics. With scale out, you need to be able to run the same process multiple times on a small scale, robustly and with the same result. With scale out, the biggest variable is often the starting materials, namely the autologous patient cells. Your process needs to be robust enough to handle variation in the starting cell population, or you need to be able to control for variation during your cell selection. ◆

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CLINICAL TRIALS

Inconsistencies Prevalent in Study Start-Up

By: Craig Morgan

INTRODUCTION

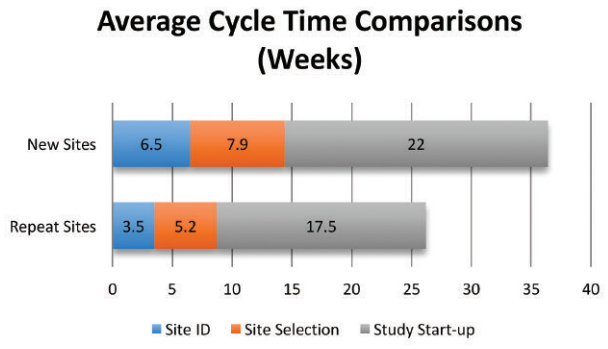
As stakeholders are increasingly aware that better study start-up (encompassing the activities associated with site identification, feasibility assessment, selection, and activation) processes are linked to shorter clinical timelines, the emphasis has been shifting in that direction.[1,2]

In a recently completed comprehensive study, The Start-Up Time and Readiness Tracking (START) II, 2017 conducted by Tufts Center for the Study of Drug Development (CSDD), a significant difference in cycle times between new versus repeat sites and organizations [sponsors versus contract research organizations (CRO)] was observed; however, the percentage of sites never activated remained at 11%, a figure that has not changed substantially in over a decade.[1] The primary reason cited was budgeting and contracting problems, which has been a challenge identified in much published work.[3] Given the new technology solutions and practices, as well as the increasing number of dedicated personnel managing site relationships, it's surprising and disappointing that the industry has not been about to make any headway in reducing the number of non-active, non-enrolling (NANE) sites.

Given the plethora of new approaches and solutions now being deployed to improve the study start-up process, the Tufts CSDD research provides a baseline upon which future studies can be conducted to gauge progress. The study was funded by an unrestricted grant from goBalto, a technology solutions provider.

The research examined a number of areas associated with study start-up, including site identification, study feasibility and recruitment planning, criteria for site selection, staffing and resources, and study start-up process improvements and opportunities.

FIGURE 1



Estimated time (in weeks) it currently takes for (initiation activity).

The respondents were composed of 403 unique organizations and three-quarters were US-based. More than half of respondents worked in sponsor companies 53% or CROs 24%, with additional responses from sites, medical device companies, and academic institutions.

Site identification cycle time was defined as the time taken to identify appropriate investigative sites. Site selection cycle time was defined as the time from site identification to feasibility and receipt of site qualification information to final site selection decision. Study start-up (also referred to as site readiness and site activation) cycle time was measured as the time that all initial sites (ie, non-backup or contingency sites) are activated or from the time the site selection decision is made until all sites are initiated and ready to enroll.

The research found that cycle times were shorter for repeat sites than they were for new sites (Figure 1). Clinical operations teams typically rely on relationships with principal investigators built over time, and while the idea of using all repeat sites might seem like a logical and sure-win way to speed study start-up it is important to point out that research suggests for a typical multi-

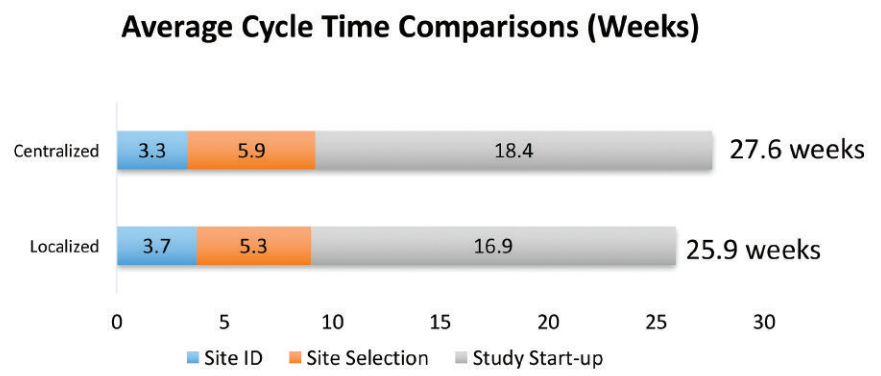
center study, 30% of sites selected are new, of which 13% are completely new to clinical research. Institutional knowledge about sites is frequently dated and soiled within departments and may not be relevant to the therapeutic area under investigation, for example, rare and orphan disease trials often require companies to work with sites and investigators they have not interacted with in the past. Moreover, study teams are blinded to problems inherent with this approach – namely, it limits opportunities to engage with new sites that could be more effective than those familiar to the study team.[4]

According to the research, companies do not use one single source of data to identify sites; a mix of non-evidence-based approaches are used, including personal networks, proprietary databases, and recommendations from study teams. Although clinical research professionals recently have been seeking access to accurate site-level performance metrics to aid investigative site identification. Use of site-level data to predict enrollment may be a more attractive option for increasing the pool of evidence available to support study start-up decision-making.[5,6]

CONSISTENCY MATTERS

If you fail to plan, you are planning to fail. These words ring true when it comes to study start-up, especially as the clinical trials sector embraces planning as key to boosting study quality. Planning works by getting it right from the beginning — prior to study activation — requiring sponsors and CROs to identify what is needed upfront to reduce risk. So, what attributes make some organizations more consistent that others in adherence to timelines and budgets?

FIGURE 2



Estimated CRO vs sponsor cycle times, repeat sites.

Only 32% of respondents were found to have consistent cycle times across all study start-up activities, completing site activation about 7 weeks earlier than other companies when working with both new and repeat investigative sites. Interestingly, respondents in the most consistent group were more likely to work with sites that are new to the organization and reported a lower percentage of non-activated sites compared to their counterparts. The most consistent groups are investing more in technology, especially in site identification, suggesting they spend greater resources on finding the right sites and they tend to be smaller companies.

SPONSORS VERSUS CROS

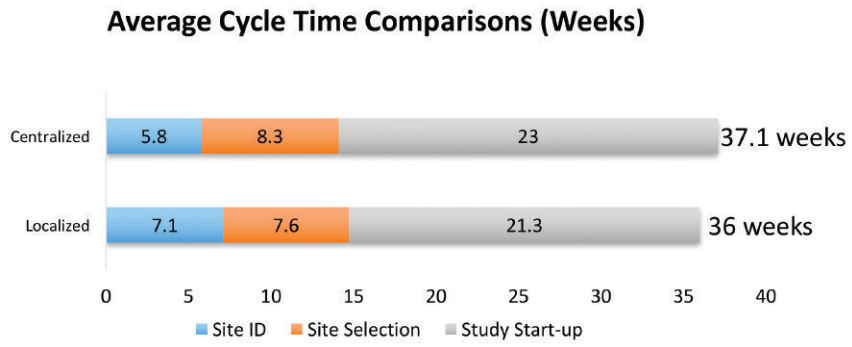
Outsourcing has become the popular way for pharmaceutical companies to utilize on-demand services, improving operational efficiencies and therapeutic expertise and adding extensive geographic capabilities. This reflects a sharper focus on core competencies and a shift to allow CROs to manage and conduct clinical trials.

More than just a fad, this trend is nothing less than a paradigm shift in the pharmaceutical industry that has struggled to contain costs and timelines associated with trials as the rescue study services industry has boomed.[7] But are CROs more efficient at study start-up?

The greatest differences were observed between sponsor and CRO practices. Cycle times reported by CROs — in comparison with those reported by sponsors — were significantly shorter: site initiation cycle times were 5.6 weeks shorter (20%) for repeat sites and 11 weeks shorter (28%) for new sites (Figures 2 and 3). Overall, CROs report completing all site related activities 6 to 11 weeks faster than sponsors.

These external service providers can achieve economies of scale unavailable to sponsors when they combine the volumes of multiple companies. Although the differences were not statistically significant, the research found that on average, CROs dedicate 18 FTEs to site selection and 30 to activation, compared with an average of 12 and 13, respectively, for sponsors. CROs also report a lower level of site non-activation at 8.7%. One potential explanation for these results is that sponsors are relying more on CROs to manage site activity, and CROs have been able to invest in more processes that would create efficiencies.

FIGURE 3



Estimated CRO vs sponsor cycle times, new sites.

ACCELERATING PROCESSES

The status of clinical trials continues to stymie industry stakeholders anxious to rein in the cost of product development and adhere to tighter timelines. Despite intense pressure to speed development, mounting evidence documents ongoing inefficiencies tied to complicated protocols, globalization, and old-school paper-based processes, driving clinical stakeholders to embrace technologies that are finally moving the needle.

But this opportunity is not without its challenges. Conducting clinical trials in places with unfamiliar regulatory pathways, cultural differences, and limited infrastructure is highlighting the value of technology that streamlines bottlenecks allowing stakeholders to better adhere to established timelines and budgets.

In the on-going pursue of cycle time reductions, what attributes are associated with the fastest companies?

The research shows that the fastest groups reach site activation (on average) in less than half the time of other companies when working with new or repeat sites. When working with repeat sites, they achieve site identification and selection 2 to 3 weeks faster, and site activation up to nearly 12 weeks faster than their counterparts. The time savings are even greater when working with new sites. Regardless of organization, centralized groups have longer cycle times; however, the differences are not statistically significant. There is no real significant difference in terms of the mix of sites (new versus repeat) that the fastest companies use compared to their counterparts.

The fastest groups are investing less in technology, suggesting they may have already achieved some cycle time advantages based on prior technology investments; nevertheless, they rely more on technology or more sophisticated tools to manage their processes than their counterparts and indicate that they are more satisfied with their current tools/technologies (reinforcing that they may be benefitting from prior investments in this area). Not surprisingly, the fastest companies tend to be smaller companies and CROs.

ORGANIZATIONAL STRUCTURE: CENTRALIZED VERSUS LOCALIZED

Study start-up is very complex and a recognized bottleneck whose functions are performed by multiple people in multiple locations at the sponsor, CRO, and site levels, all of whom need to communicate and share data. To make this happen, dedicated systems integrated with other clinical trial technologies is essential, but what about the organizational structure of clinical operations teams? Do centralized groups outperform non-dedicated groups?

According to the research, centralized functional groups report slightly higher satisfaction with their processes, reporting larger time savings, and appear to adopt technology more, whereas decentralized or localized functional groups report slightly better cycle times with new (3% faster) and repeat (6.2% faster) sites.

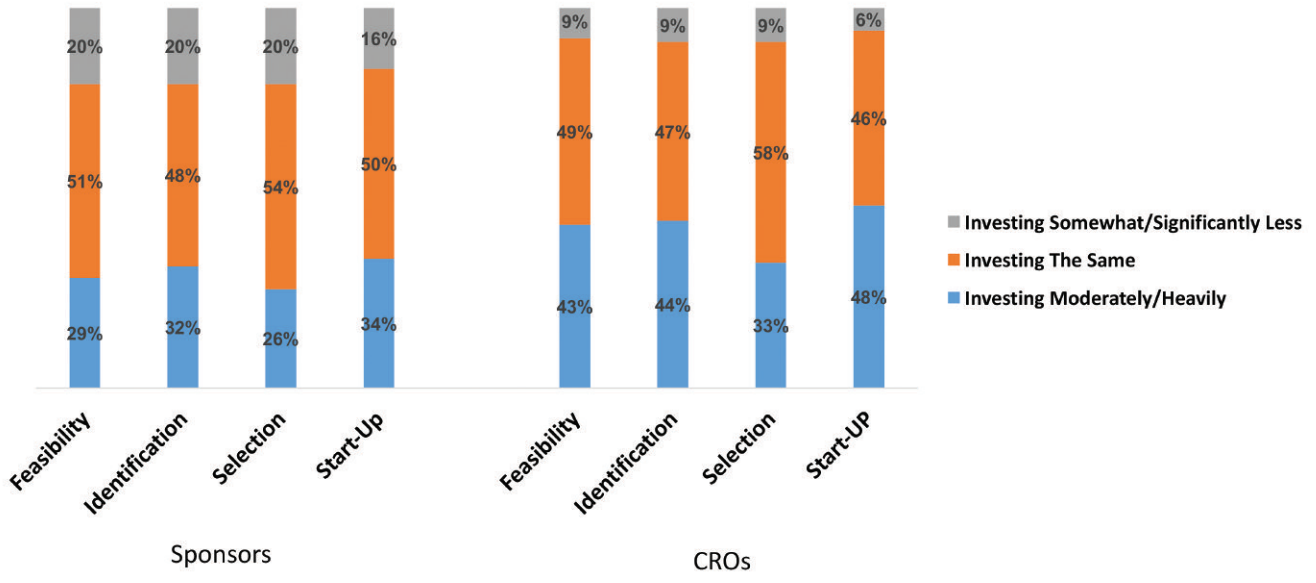
Irrespective of organizational structure, both groups face similar challenges and see the same opportunities for improvement. There is no conclusive evidence that centralizing the function of site identification through to site activation achieves significant improvements.

TECHNOLOGY & PROCESS IMPROVEMENTS

Many of the improvement areas cited involve new technologies or changes in organizational processes and require a great investment of resources and time. Despite many attempts at improvement within organizations, gains in end-to-end cycle time have not been made.

Practices intended to streamline study start-up timelines include the use of technology investments to expedite the collection of clinical data and to help sponsors/CROs better monitor clinical trial performance. New technologies include predictive analytics and site forecasting for investigator identification, automated online site feasibility and site scoring system for faster turnaround time, and electronic

FIGURE 4



The extent to which respondents are investing in additional technology to support (initiation activity).

document exchange repositories to speed up essential document collection.[8] Many sponsors and CROs have also implemented clinical trial management systems (CTMS), electronic cloud-based solutions and online clinical document exchange portals.9 Shared investigator databases are another resource that organizations are utilizing.

CRO and sponsor subgroups also differ in technology investment. On average, those working at CROs are investing about 10% more frequently in all areas of study initiation (identification, feasibility, selection, and study start-up [ie, activation)] and more frequently invest moderately to heavily across all areas when compared with sponsors (Figure 4).

According to the research, 80% of respondents who have invested in technology report time savings. Respondents reporting their technology is adequate have 30% shorter cycle times than those with inadequate technologies.

On average, 10% of respondents reported they are very satisfied with their study start-up processes, whereas 30% to 40% expressed dissatisfaction. Respondents reporting that they are very satisfied have cycle times 75.5% shorter than those reporting they are completely unsatisfied. Overall, nearly 40% of respondents of respondents are still using unsophisticated methods (eg, excel, paper-based systems), which may contribute to lower satisfaction levels.

Respondents were largely aligned on what measures would be most effective at enhancing various study start-up activities. The top cited option for enhancing site identification was "pooling and sharing data on site performance" with 88.9% of respondents indicating it would enhance the process, for site selection, the top cited option was to "get better evidence of a site's true potential before selection" at 95.7%, and for activation process enhancements "central IRB/Ethics approval process" at 94.5%.

This research presents new benchmark metrics on the comprehensive cycle time from site identification through site activation. Overall, the study start-up process is still very long — 5 to 6 months total duration on average — a figure that has not improved throughout the past decade.

There is still a pervasive need for effective solutions across the industry despite many commercially available options (IMS Study and Site Optimizer, TransCelerate Shared Investigator Platform, and Investigator Databank) and internal solutions (eg, internal investigator dashboards and site feasibility software).[10]

There is wide variation and inconsistency in study start-up practices within and between sponsor companies.11 Given the high cost of initiating one site, which has been estimated at $20,000 to $30,000 plus another $1,500 per month to maintain site oversight, the prevalence of delays, and inefficiencies associated with study start-up activity, sponsor and CROs are continually looking to improve their study start-up cycle times.

The full report, subsequent mini-reports, as well as the groundbreaking START research conducted in 2012, are

available for download from the goBalto Resource Center (https://www.gobalto.com/resource-center). ◆

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BIOGRAPHY

Craig Morgan is a technology and life sciences management professional with more than 15 years of experience in the application of informatics and bioinformatics to drug discovery. He currently heads up the Marketing and Brand Development functions at goBalto, working with sponsors, CROs, and sites to reduce cycle times and improve collaboration and oversight in clinical trials.

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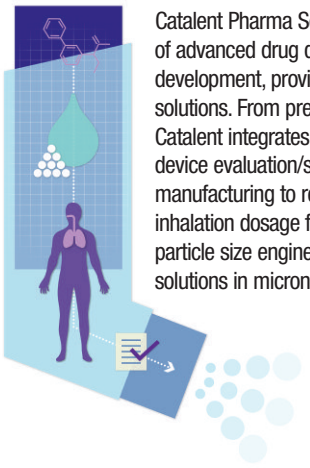

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Showcase

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EPR SPECTROSCOPY

Bringing EPR to a Wider World: Biological ROS & RNS Detection

By: Kalina Ranguelova, PhD

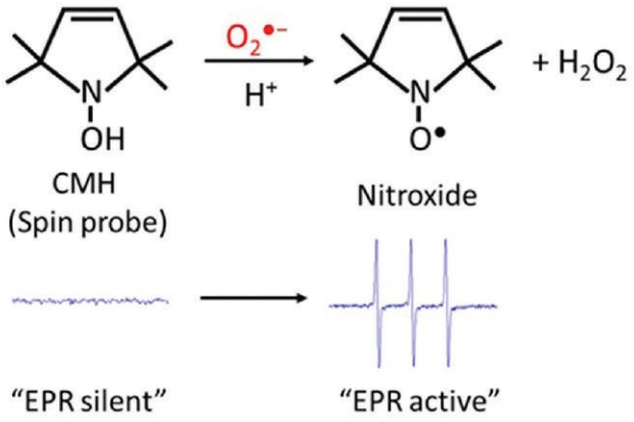
INTRODUCTION

Oxidative stress and damage in cells is associated with the development of cancer, Alzheimer's disease, atherosclerosis, autism, infections, and Parkinson's disease. Reactive Oxygen Species (ROSs) are the main cause of oxidative stress and damage in cells, causing damage to proteins, lipids, and DNA. As existing therapies for such diseases can be ineffective, there is a need for the development of novel drugs based on new targets.

The major reason to measure ROS and Reactive Nitrogen Species (RNS) in biological systems is to determine whether they play a role in physiological or pathophysiological processes. Detection and characterization of radicals in biological materials is most commonly done using EPR (electron paramagnetic resonance) methodology. EPR spectroscopy applications span across a wide range of areas from quality control to molecular research in fields such as material research, structural biology, and quantum physics. Most of the biologically relevant radicals are very short lived and, therefore, impossible to detect in biological samples. For this reason, compounds (spin traps and spin probes) have been used that form stable adducts with radicals (Figure 1). Unfortunately, quite often the spin traps have low reactivity with ROS, and the formed radical adducts are very susceptible to bio reduction when exposed to cells or tissues that converts them to EPR silent species.

In this article, we determine the challenges associated with ROS detection and highlight three examples of how EPR can be used to understand the free-radical process. Additionally, it will demonstrate how the latest digital and microwave technologies in benchtop EPR instrumentation is giving researchers new insight into ROS and free radicals that may shape the future development of more effective treatments of disease.

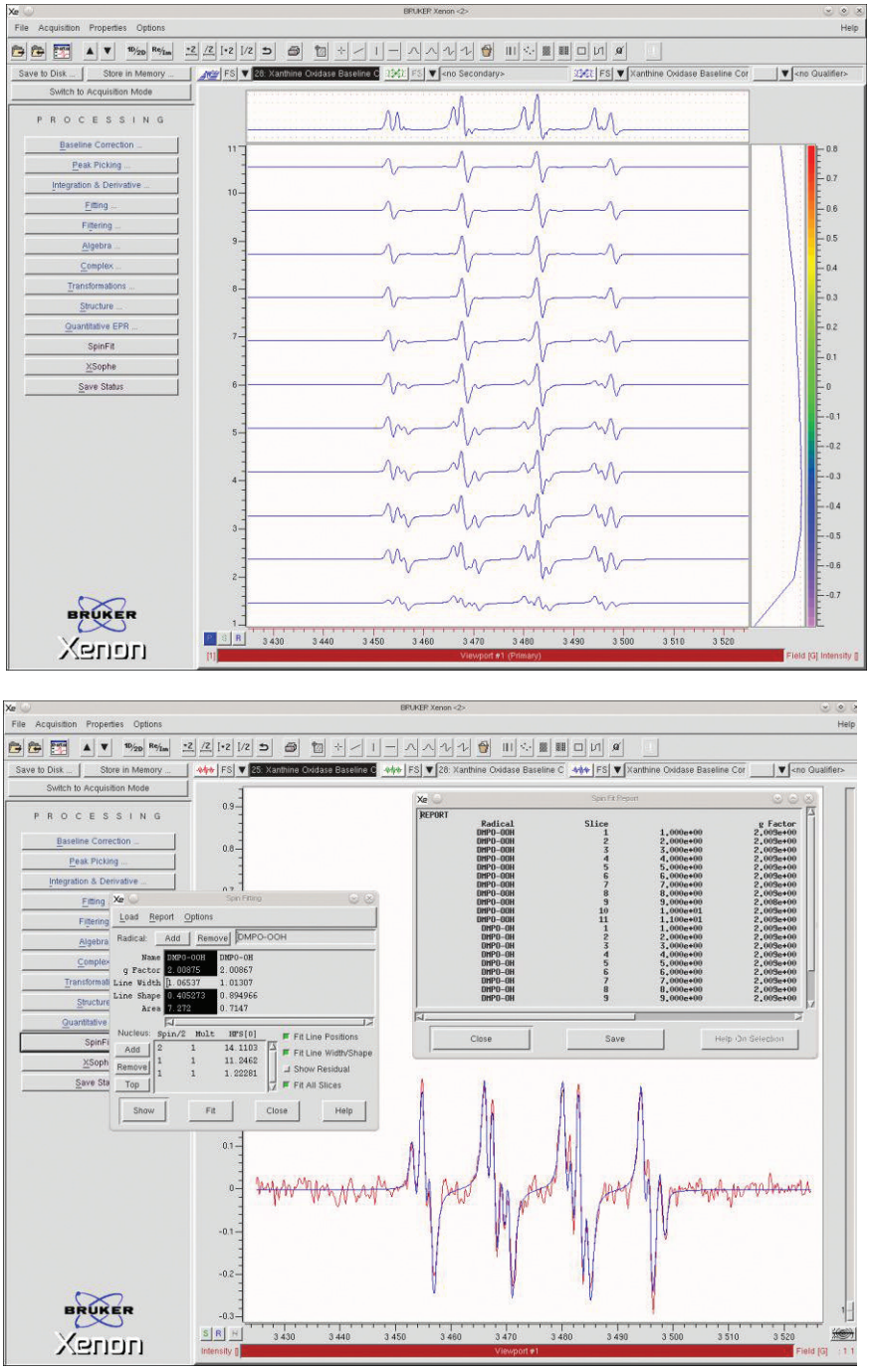
FIGURE 1



WHY IS STUDYING ROS IMPORTANT?

The interest in free radical processes in living systems has increased exponentially throughout the past decade. The huge complexity of the evolved processes makes necessary the analysis of the problem from a fundamental point of view. Radicals are intermediates in a variety of biochemical reactions. Some of the most abundant radicals produced in natural biochemical reactions are ROS such as hydroxyl, hydroperoxyl, and superoxide radicals, and RNS, such as nitrogen monoxide and peroxynitrite. The rapid and rigorous detection and quantification of free radicals will lead to a better understanding of the chemical biology and will also help in the discovery of specific inhibitors. Identifying sources of excessive, defective, or unbalanced ROS and RNS levels and developing alternative strategies to regulate their respective levels should help in designing novel rational therapies.[1]

FIGURE 2



Experimental data (red) and SpinFit simulations (blue) of DMPO radical (superoxide and hydroxyl) adducts in Xanthine/Xanthine oxidase system at a given time in the 2D Field versus Time experiment. Defining the DMPO radical adducts in the SpinFit dialogue by import from library database.

EPR FOR BIOMEDICAL APPLICATIONS

Direct detection of ROS and RNS is very difficult or impossible in solution at room temperature due to their very short half-lives. EPR is the only method for the direct detection of paramagnetic species. EPR experiments have provided invaluable information pertaining to metallo-protein structures and to the structures and processes in photosynthesis. In biology, EPR can be applied to the study of membrane proteins, metallo-enzymes, IDPs, RNA, DNA, spin labelling/trapping, nitric oxides, and ROS & RNS. Overcoming the identification of ROS is a key driver for the development of effective treatments of disease. No matter what the focus of the application is, the crucial required strengths of an EPR spectrometer are sensitivity and stability. Innovations in magnet and microwave technology helps to deliver enhanced performance, addressing the needs of researchers for both ease of use with high quality EPR data.

EPR is used for both static and dynamic investigations of materials, chemicals, and biological systems, including molecular radical structures and formation. EPR is advantageous for dynamic measurements as an EPR spectrum can be measured while applying changes in conditions, such as temperature or light irradiation. Applications include polymer synthesis, testing the purity of silicon in solar cells, spin trapping to assess the oxidative stability of flavors, and the analysis of metallo-proteins. In electrochemistry, redox chemistry, photochemistry, and catalysis, EPR can be used to study metal centers and radicals involved in chemical processes.

New applications have revived interest in EPR as an analytical tool for chemistry, materials science, and biology, where scientists and researchers have uncovered the benefits of utilizing newer compact, yet high-performance EPR benchtop instruments. Benchtop EPR spectrometers can be used to analyze many EPR samples, including transition metals, antioxidants, and free radicals, providing valuable information and insights into biological and chemical systems. Newer benchtop instruments, such as the EMXnano from Bruker, benefits from an integrated novel, permanent magnet and an

efficient new microwave resonator to deliver sensitivity and stability in a benchtop EPR system, making it suitable for a wide range of analyses, teaching applications, as well as for quantitative EPR with the inclusion of a spin counting module.

New-generation magnet systems and efficient microwave resonators enable accurate results and superior sensitivity in benchtop form. This enables research, teaching, or process applications to benefit from EPR spin trapping spectroscopy. It also enables researchers and students with limited EPR experience to use the power of EPR spin trapping spectroscopy to identify and quantify free radicals in biological systems (proteins, blood, tissues, cells, etc).

APPLICATION EXAMPLES

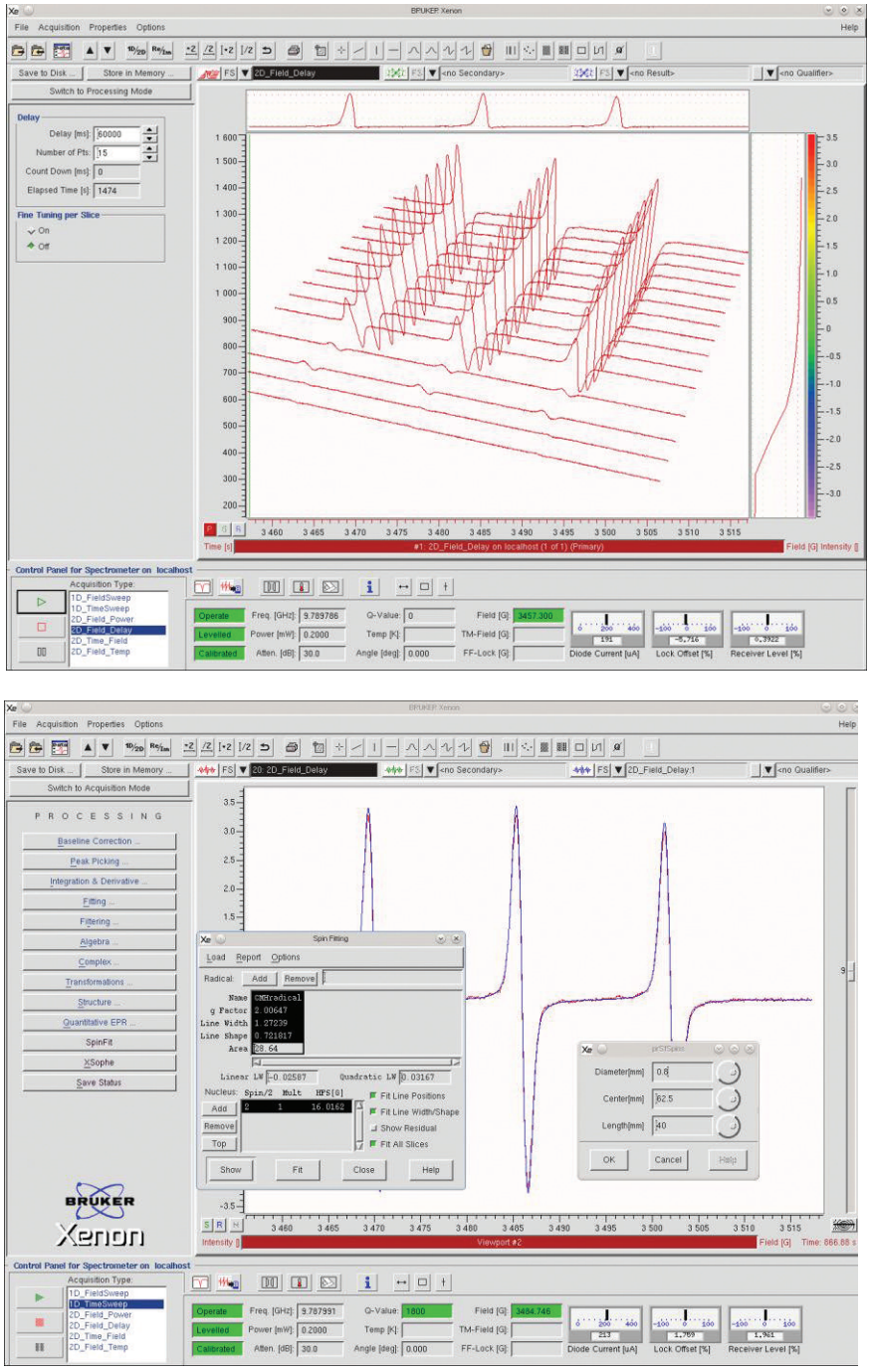
The following applications demonstrate how EPR spectroscopy (also known as electron spin resonance, ESR, spectroscopy) can be utilized for the detection and characterization of radicals in biological systems.

Quantitative EPR Spin Trapping Application

As discussed, direct detection of ROS and RNS is very difficult or impossible in solution at room temperature due to their very short half-lives. Two leading ROS are radicals such as the superoxide radical (O_2•–) and the hydroxyl radical (•OH) as shown here in the Xanthine/Xanthine oxidase system (Figure 2), where their generation and decomposition can be accurately followed with quantitative EPR.

EPR spin trapping is a technique developed in the late 1960s in which a nitrone or nitroso compound reacts with a target free radical to form a stable and distinguishable free radical that is detected by EPR spectroscopy. The spin trapping reaction involves the addition of the reactive free radical to the double bond of a diamagnetic "spin trap" to form a much more stable free radical, which can then be examined with EPR. This "radical adduct" has spectral features that allow easy identification of the reactive radical originally generated.

FIGURE 3



Formation of CM• nitroxide as a function of time in the 2D Field versus Time experiment due to the reaction CMH + O_2•- –> CM• + H_2O_2. SpinFit and SpinCount modules provide ROS concentration for quantitative EPR analysis at any given time point during the reaction.

EPR Spin Probes Application

In vascular cells, increased generation of superoxide (O_2•–) has been suggested

to occur in hypertension, diabetes, and heart failure. Thus, the accurate detection and ability to quantify $O_2^{\bullet-}$ are critically important in understanding the pathogenesis of these various cardiovascular disorders and other non-cardiovascular diseases. However, direct detection of ROS and RNS is very difficult or impossible in solution at room temperature due to their very short half-lives. As shown in Figure 3, the generation of superoxide over time can be easily monitored with a bench-top EPR spectrometer.

Spin probes are not spin traps, in that they do not "trap" radicals, but they are oxidized to form nitroxides (free radicals) with a half-life of several hours, which can readily be detected by EPR (Figure 1). For example, the cyclic hydroxylamine 1-hydroxy- 3-methoxycarbonyl-2,2,5,5-tetramethylpyrrolidine (CMH) can provide quantitative measurements of superoxide ($O_2^{\bullet-}$) with high sensitivity and it has been used for detection of intracellular $O_2^{\bullet-}$ in cultured cells and tissue samples.

Bench-top EPR spectrometers can be used effectively for mechanistic studies and kinetic analysis of multiple radicals (ROS and RNS) generated in enzyme reactions. Properly controlled spin probe experiments can verify that the formation of radical adducts is due to free radical production in the reaction system being studied.

Nitric Oxide Application

Human skin contains photolabile nitric oxide (NO) derivatives, which upon UVA radiation, decompose under high-output NO formation and exert NO-specific biological responses, such as increased local blood flow or reduced blood pressure. The intradermal increase of free NO due to blue light irradiation of human skin can be monitored and quantified using EPR.

Nitric Oxide (NO) is a highly reactive

regulatory molecule which has many important physiological roles, such as a neurotransmitter in the central nervous system, a regulator of vasomotor tone in the cardiovascular system, and a cytotoxic mediator of the immune system. NO is a free radical, and its short half-life (< 30 sec) has rendered direct measurement difficult. The instability of NO can be overcome by using a NO-trapping technique, in which a more stable complex is formed and subsequently detected by EPR. For example, the oxidation of nitric oxide (NO) to nitrate by oxyhemoglobin (oxyHb) is a fundamental reaction in NO biology and binding of NO to the heme can be characterized by EPR.

EPR provides the means to detect NO by both room temperature and low temperature techniques with high sensitivity. With accessories for room temperature and low temperature measurements, detection of NO with MGD (N-methyl-D-glucamine dithiocarbamate) or hemoglobin as a spin trap is easy to achieve.

BENCH-TOP EPR

Benchtop EPR spectrometers have been designed with users in mind, who require research performance and ease of use. A benchtop instrument provides many features typically found only on sophisticated, floor-standing EPR instruments, making research-grade EPR capabilities accessible to a broader range of scientists. Benchtop instruments often include defined workflows for easy and fast system setup, with user-friendly interfaces that allows parameters to be easily adjusted also by non-EPR experts.

SUMMARY

As the global demand for novel cures for illnesses continues to rise - driven largely by the high mortality rates and increased healthcare costs associated with diseases - researchers are focusing their studies on the disease dynamics. EPR is at the forefront of the revolution, widely considered to be the "gold standard" for the detection and characterization of radicals in biological systems.

The positive aspects of EPR spectroscopy and associated methodologies can be used to maximize useful information, and minimize artefacts, when used in biological studies. This technique can provide a wealth of valuable information on the presence of radicals and some transition metal ions in biological systems. It can provide definitive information on the identity of the species present and also information on their concentration, structure, mobility, and interactions.

The technique is already being used to inform research in a number of clinical areas, most significantly in disease research fields such as cancer, Alzheimer's disease, atherosclerosis, autism, infections, and Parkinson's disease. EPR remains a definitive method of identifying radicals in complex systems and is also a valuable method of examining radical kinetics, concentrations and structure. Looking forward, these innovations will surely put more powerful data into the hands of researchers, further accelerating the development of drugs and informing clinical practice.◆

REFERENCE

1. Rouaud F, et al. Regulation of NADPH-dependent nitric oxide and reactive oxygen species signalling in endothelial and melanoma cells by a photoactive NADPH analogue. Oncotarget. 2014;5(21):10650-10664.

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BIOGRAPHY

Dr. Kalina Ranguelova is an EPR Applications Scientist in Bruker BioSpin Corporation since 2011. She earned her PhD at The Bulgarian Academy of Sciences, where she focused her research on inorganic copper complexes structure using electron paramagnetic resonance (EPR) spectroscopy. After two research positions at CUNY and NIH, where she studied free radical biology and EPR spin trapping as method for measurement of reactive oxygen species (ROS), she joined Bruker and holds a role as Applications Scientist. Her current focus is detection and identification of free radicals in biological systems and pharmaceuticals using spin traps and spin probes. She has publications in journals, including Journal of Biological Chemistry, Biochemistry, Free Radical Biology and Medicine, etc., and has presented in many international meetings related to free radical research in biology and protein chemistry.

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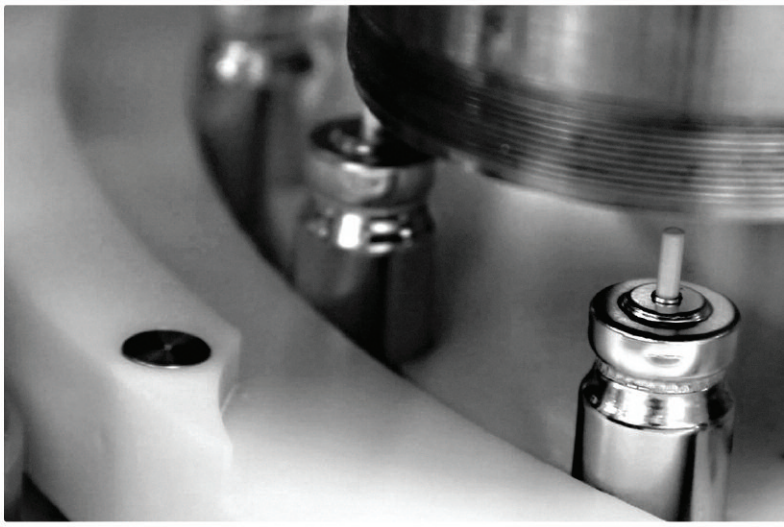

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