Drug Development & Delivery

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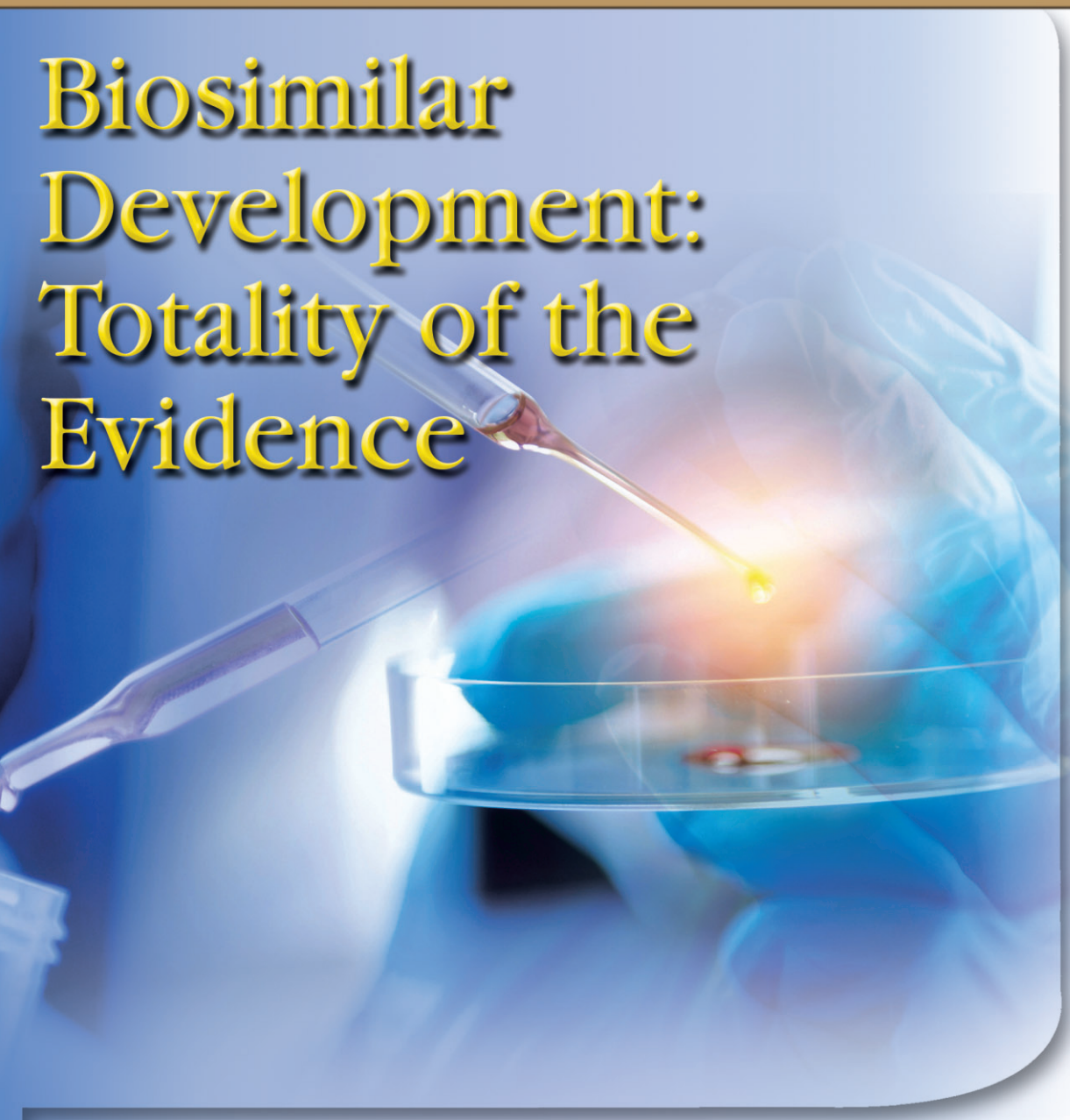
Biosimilar Development: Totality of the Evidence



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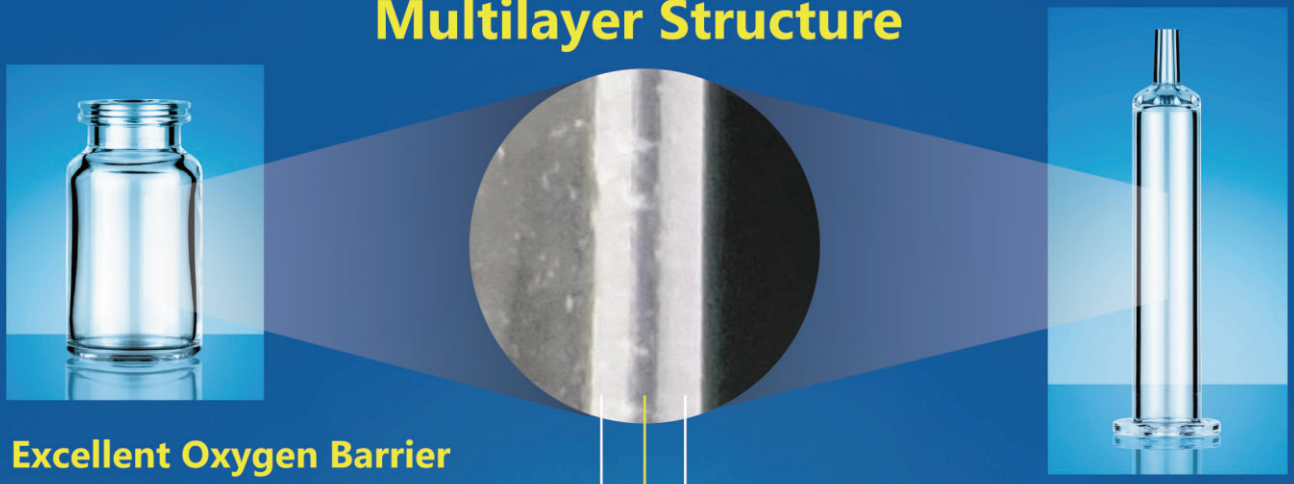

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Corporate/Editorial Office
219 Changebridge Road, Montville, NJ 07045
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1 BD Intevia™ design specifications. Pont-de-Claix, France: Becton Dickinson and Company; 2017.
2 BD Intevia™ analysis report: injection time for viscous solution. Pont-de-Claix, France: Becton Dickinson and Company; 2017.

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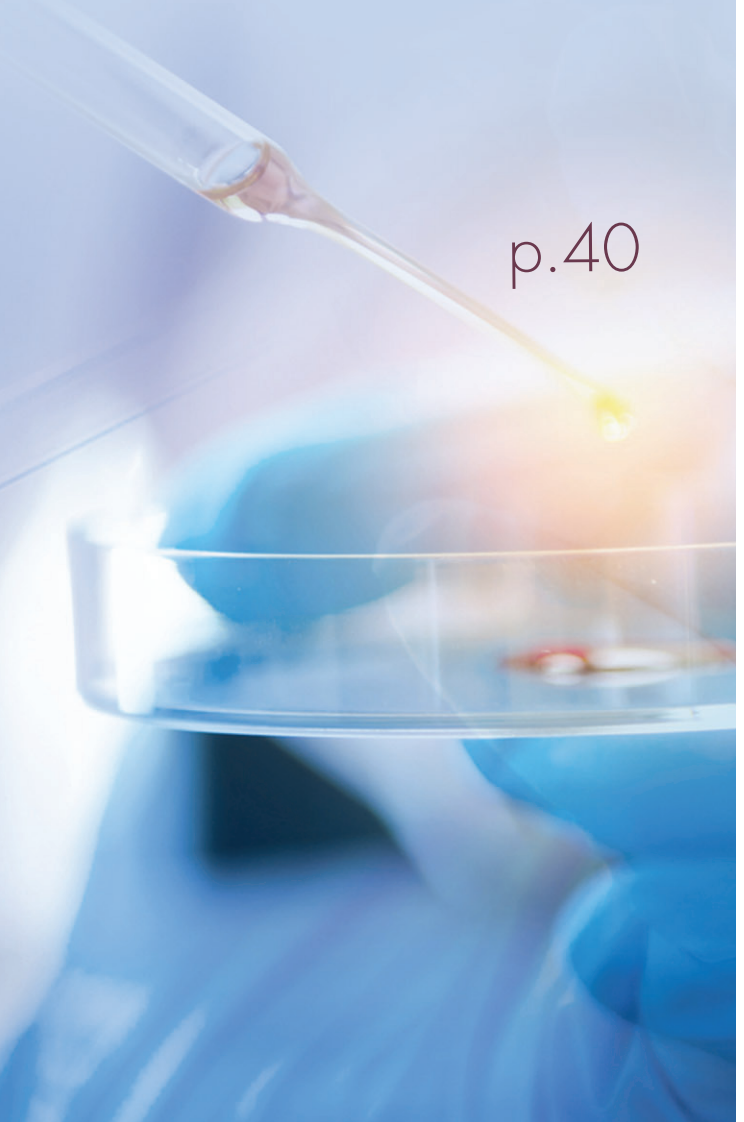
Totality of the Evidence

"Unlike new medicines that are approved on the basis of extensive clinical data, often in multiple indications and in different patient populations, biosimilar medicines are developed using the concept of totality of the evidence."



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A Shift Toward Specialization

"As drug products become more complex, there is increasing customer demand for relationships with CDMOs that have core competencies in highly specialized formulation and process technology areas. One of these specialty areas is complex molecules. Biotech companies developing novel biologics are increasing in the market, thus there is an increase in outsourcing development services to BioCDMOs."

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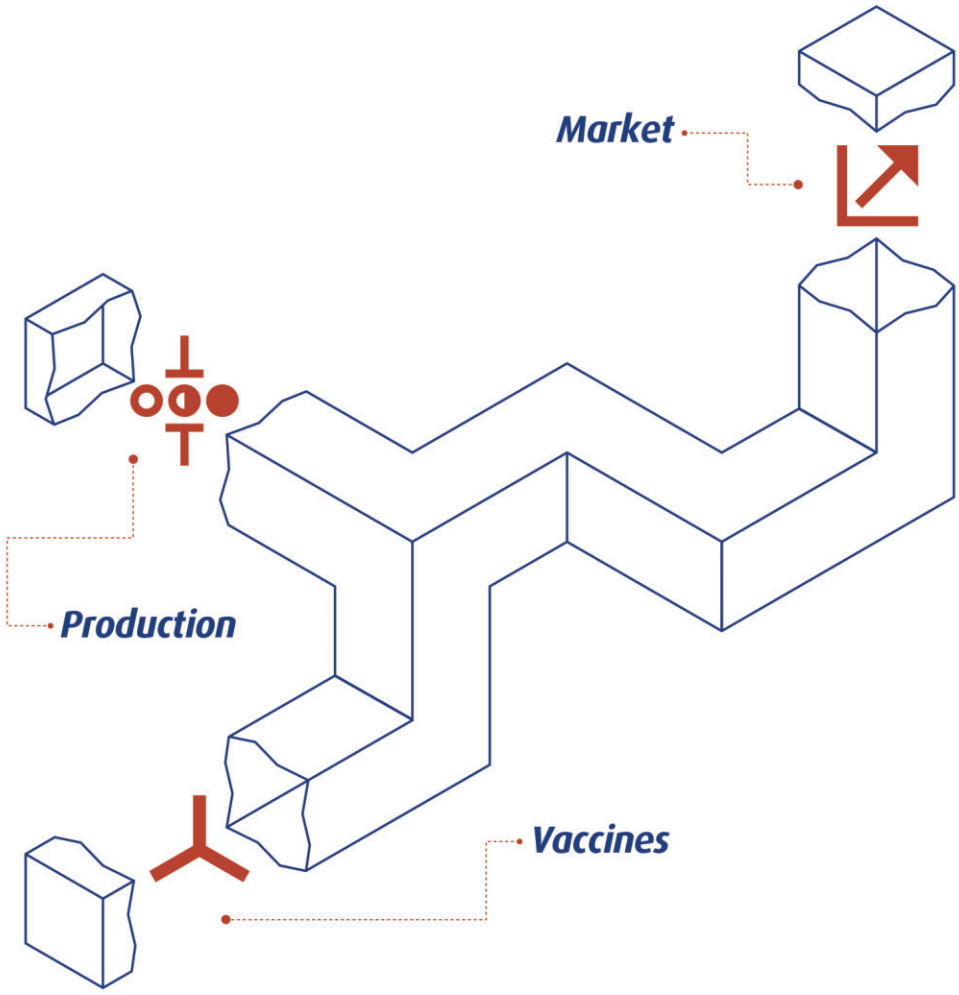
THE COMPLEX MADE SIMPLE



CDMO SERVICES FOCUSED ON BRINGING VACCINES TO MARKET

Bavarian Nordic is a globally integrated biotechnology company focused on in-house executed research, development, manufacturing and marketing of innovative and safer vaccines against cancer and infectious diseases for which the unmet medical need is high and for which we can harness the power of the immune system to induce a response.

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BAVARIAN NORDIC

Crinetics Pharmaceuticals Initiates Phase 1 Study for Treatment of Neuroendocrine Tumors

Crinetics Pharmaceuticals, Inc. recently announced the initiation of a Phase 1, double-blind, randomized, placebo-controlled, single- and multiple-dose study to evaluate the safety, pharmacokinetics, and pharmacodynamics of CRN01941 in healthy volunteers. CRN01941 is an oral nonpeptide somatostatin receptor subtype 2 (sst2) biased agonist designed for the treatment of neuroendocrine tumors (NETs) that originate from neuroendocrine cells commonly found in the gut, lung, or pancreas.

"Crinetics is dedicated to building a pipeline of novel therapeutics for rare endocrine diseases and endocrine-related tumors. We are excited to advance CRN01941, our second product candidate, into the clinic," said Alan Krasner, MD, Chief Medical Officer of Crinetics. "CRN01941 has the potential to be an orally-administered treatment for patients struggling with NETs. Although these tumors are typically slow growing, they are also often metastatic resulting in significant morbidity and mortality."

This Phase 1, double-blind, randomized, placebo-controlled, single-dose and multiple-dose study of CRN01941 will enroll up to 119 healthy male and female subjects. This single-center study will be conducted in 3 parts: a single-ascending dose phase (up to 8 cohorts, 8 subjects/cohort), a multiple-ascending dose phase (up to 5 cohorts, 9 subjects/cohort), and single dose phase in elderly subjects (1 cohort, 10 subjects). The primary objectives of the study are to evaluate the safety, tolerability, and pharmacokinetics of single and multiple doses of CRN01941. Additional information about the trial can be found on ClinicalTrials.gov using the identifier NCT03936166.

NETs arise from cells of the enteroendocrine system in the gastrointestinal tract (approximately 70% of cases) but can also arise from neuroendocrine cells in the lung (approximately 25% of cases) or, more rarely, the pancreas. In approximately 10% to 20% of cases, these tumors are associated with excess secretion of serotonin resulting in carcinoid syndrome, which is characterized by severe diarrhea and flushing. Patients with well- and moderately differentiated tumors and distant metastases have a 5-year survival probability of ranging from 30% to 70%. NETs are present in approximately 171,000 adults in the US and while still an orphan disease, it is the second most common gastrointestinal malignancy after colon cancer.

Crinetics Pharmaceuticals is a clinical-stage pharmaceutical company focused on the discovery, development, and commercialization of novel therapeutics for rare endocrine diseases and endocrine-related tumors. The company's lead product candidate, CRN00808, is an oral selective nonpeptide somatostatin receptor type 2 biased agonist undergoing two Phase 2 clinical trials for the treatment of acromegaly, an orphan disease affecting more than 25,000 people in the US. Crinetics' second oral product development candidate, CRN01941, has entered the clinic for the treatment of neuroendocrine tumors. The company is also developing oral non-peptide somatostatin agonists for hyperinsulinism, as well as oral nonpeptide ACTH antagonists for the treatment of Cushing's disease. For more information, visit www.crinetics.com.

Catalent Completes Acquisition of Gene Therapy Leader for $1.2 Billion

Catalent, Inc. recently announced it has completed the $1.2-billion acquisition of Paragon Bioservices, Inc., a leading viral vector development and manufacturing partner for gene therapies.

With the addition of Paragon's specialized expertise in adeno-associated virus (AAV) vectors, the most commonly used vector to deliver DNA to cells, Catalent is positioned to capitalize on strong industry tailwinds in the potentially $40-billion addressable market for gene therapies. Paragon also brings to Catalent its unique and differentiated scientific, development, and manufacturing capabilities, which will fundamentally enhance Catalent's biologics business and end-to-end integrated biopharmaceutical solutions for customers.

Paragon recently announced the opening of its new, state-of-the-art commercial manufacturing center near the Baltimore-Washington International (BWI) airport, which is equipped with several 500-liter and 2,000-liter single-use bioreactors for clinical through commercial material production. The new large-scale production campus – now combined with a recently leased second building which will be built out for commercial GMP manufacturing – has the potential for more than 425,000 square feet of manufacturing space upon completion.

Paragon has GMP manufacturing projects underway with more than half of the top 40 leading gene therapy developers worldwide. Catalent is committed to continuing the resource dedication for Paragon's customers and maintaining a flexible and reliable development and manufacturing partnership for its clients. The company currently employs over 380 individuals at its two Baltimore-area sites, all of whom will join the existing Catalent team of over 11,000 employees.

In connection with the acquisition of Paragon, Catalent Pharma Solutions, Inc., as borrower, and certain other wholly owned subsidiaries of Catalent entered into an amendment, dated as of May 17, 2019, to its existing credit agreement with JPMorgan Chase Bank, N.A., as administrative agent and collateral agent, to provide for, among other things, $950 million of incremental term loans and a $350 million increase to its revolving credit facility. The proceeds of the incremental term loans were used to fund a portion of the acquisition consideration and for general working capital purposes, to pay fees, costs, and expenses incurred in connection with the transactions contemplated hereby, for capital expenditures of Paragon and to prepay a portion of the existing term loans.

Also in connection with the acquisition of Paragon, Catalent completed the issuance of $650 million of a new series of convertible preferred stock to funds affiliated with Leonard Green & Partners, L.P. Effective as of the closing of the acquisition, Peter Zippelius, a partner at Leonard Green & Partners, joined Catalent's Board of Directors.

Catalent is the leading global diversified provider of advanced delivery technologies and development solutions for drugs, biologics, and consumer health products. Catalent Biologics provides advanced technologies and integrated solutions for biologic development and manufacturing, including antibody-drug conjugates (ADCs), bi- and multi-specific antibodies, biosimilars, and gene therapies, from DNA to fill/finish and commercial supply.

Owlstone Medical Enters Strategic Collaboration With Actelion

Owlstone Medical recently announced a strategic collaboration with Actelion Pharmaceuticals Ltd, one of the Janssen Pharmaceutical Companies of Johnson & Johnson and a global leader in pulmonary arterial hypertension (PAH), to discover and validate a breath-based test to help facilitate the early diagnosis of pulmonary hypertension and its subtypes. This development program will be solely funded by Actelion.

Pulmonary hypertension (PH) is a progressive cardiopulmonary disease in which the blood pressure increases in the vessels that transport blood from the heart to the lungs, placing strain on the right side of the heart and often leading to heart failure. Unfortunately, early diagnosis of PH is very difficult, and even at an advanced stage presents similar to other heart and lung conditions, so a delay of years between the onset of symptoms and diagnosis and treatment is common. There is therefore an urgent need for effective tools to facilitate screening and early diagnosis of patients presenting with early signs of PH and its sub-groups.

The collaboration will initially involve collecting breath exhaled Volatile Organic Compounds (VOCs) from over 1,000 patients using Owlstone Medical's proprietary sampling device, ReCIVA from sites in the UK, US, and other countries in the EU. These VOCs will be analyzed by Owlstone Medical to identify those that are associated with PH, in order to develop biomarker signature(s) that can help facilitate earlier detection of the disease.

"Owlstone Medical was founded with the objective of improving the early diagnosis of disease in order to save lives through the application of Breath Biopsy. This strategic collaboration with Actelion, which is focused on improving the lives of those suffering from PH and PAH, represents a tremendous opportunity to do just that. This is particularly true in underdiagnosed areas such as PH, where early diagnosis is difficult and so screening has to be simple, reliable, and cost effective. We believe Breath Biopsy will deliver a program from discovery through to the launch of a test to the market, and this novel approach will make a real difference for the healthcare of patients suffering from PH," said Billy Boyle, Co-founder and CEO at Owlstone Medical.

Pulmonary hypertension (PH) is a progressive lung disease where the blood vessels that transport blood from the heart to the lungs narrow and become stiff, causing the blood pressure in them to rise above normal levels. This in turn places strain on the right side of the heart as it works harder to supply the lungs with blood and over time, the muscle of the heart can weaken leading to heart failure. Unfortunately, PH is difficult to diagnose early as it is seldom detected in a routine physical exam, and even at an advanced stage clinical presentation is similar to that of other heart and lung conditions and so a delay between the onset of symptoms and diagnosis of years is common.

Saama Challenges Analytics Industry to Guarantee Data Platforms to Help Accelerate Drug Development

Saama Technologies, Inc. recently issued a call-to-action on Clinical Trials Day urging the analytics industry to commit to timely deployment of solutions for biopharmaceutical companies and the elimination of launch delays that too often hinder clinical operations. Saama launched its new Product Guarantee as the vanguard of this challenge, pledging to its biopharmaceutical partners a 4-week timeline for activation and access to the out-of-the-box capabilities of its award-winning Life Science Analytics Cloud (LSAC).

"Time and again, Saama has heard our life science clients express frustration regarding promises made by technology vendors about timelines that were never met, leading to unsuccessful launches that delayed clinical progress," said Joe Ehrline, Vice President of Sales at Saama Technologies. "Data analytics should facilitate, not hamper, clinical development. Saama's Product Guarantee will establish an industry standard for delivering actionable business insights in a defined period of time that will help move the clinical development needle forward, while minimizing risk."

"The life science industry has historically struggled with and been very dissatisfied by the discrepancy between the promise of data analytics activation timelines and the reality of inevitable, associated delays," said Alan S. Louie, PhD, Research Director, Life Sciences, IDC. "We welcome Saama's Product Guarantee, and hope that the company's call-to-action reverses this trend and leads to similar commitments from other data analytics providers."

Saama's Product Guarantee is facilitated by the easy-to-use LSAC platform, an AI-powered platform disrupting the planning, designing, and conduct of clinical trials across various stages of clinical development. The platform's flexibility drives its speed of deployment and makes it easy to configure. LSAC seamlessly ingests, integrates, curates, and harmonizes clinical trial operational and patient data from proprietary and external data sources to deliver actionable, regulatory-ready insights. LSAC's novel deep learning approach significantly compresses clinical program timelines from clinical plan development to submission judgment for a New Drug Application (NDA).

For further details about the Saama Product Guarantee, contact: product-guarantee@saama.com.

Saama Technologies is the advanced clinical data and analytics company, unleashing wisdom from data to deliver better actionable business outcomes for the life sciences industry. Saama's unified, AI-driven clinical data analytics cloud platform seamlessly integrates, curates, and animates unlimited sources of structured, unstructured, and real-world data to deliver actionable insights across all therapeutic areas. The award-winning platform gives unprecedented real-time visibility into clinical data, enabling sponsors to file New Drug Applications (NDAs) more efficiently to bring drugs to market faster and at lower costs. For more information, visit http://www.saama.com.

Precision Therapeutics' Helomics Division Selected by AccuGenomics as Preferred Lab Partner

Precision Therapeutics Inc. recently announced its Helomics division has been selected as the preferred laboratory to provide laboratory services for the recently funded National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) grant to develop test kits, which will be branded as Accukit, for screening of microbial and viral contamination of biopharmaceuticals with its partner AccuGenomics, Inc. The Accukit development is in partnership with AccuGenomics, Celgene, Merck, and North Carolina State University (NCSU) with the goal of improving biosafety testing for biopharmaceutical products.

"The opportunity to contribute to innovative approaches to drug development is an important part of our business. Having received the highest inspection marks from NYSDOH and California, our state-of-the-art and highly recognized CLIA-certified lab in Pittsburgh contributes to our remaining at the cutting edge of innovation with leading edge partners that utilize our boutique contract research services," said Gerald Vardzel, President of Helomics. "We are particularly pleased to be working as the preferred laboratory in conjunction with such notable partners as AccuGenomics, Celgene, Merck, and NCSU in creating these biosafety test kits."

According to the grant proposal, Helomics will collaborate with AccuGenomics to develop an innovative, highly sensitive Next Generation Sequencing (NGS)-based testing platform to streamline screening of microbial and viral contamination of biopharmaceuticals. The Accukit will be able to detect 22 known adventitious viruses and bacteria at sensitivity levels required to pass strict Quality Control standards. The platform is also easily extendable to detect potential new contaminating agents.

"Collaborating with Helomics on this development program provides significant confidence to all participants in achieving a successful outcome, and we are pleased to have them as our preferred laboratory for providing quality NGS services," added Nick Lazaridis, CEO of AccuGenomics. "Their unparalleled expertise, coupled with their high-quality laboratory and bioinformatics services have created an excellent partnership environment from which we expect superior results."

Precision Therapeutics operates through its three wholly owned subsidiaries, Helomics, TumorGenesis and Skyline Medical. Helomics applies artificial intelligence to its rich data gathered from patient tumors to both personalize cancer therapies for patients and drive the development of new targeted therapies in collaborations with pharmaceutical companies. Helomics' CLIA-certified lab provides clinical testing that assists oncologists in individualizing patient treatment decisions, by providing an evidence-based roadmap for therapy.

In addition to its proprietary precision oncology platform, Helomics offers boutique CRO services that leverage its TruTumor, patient-derived tumor models coupled to a wide range of multi-omics assays (genomics, proteomics, and biochemical), and an AI-powered proprietary bioinformatics platform (D-CHIP) to provide a tailored solution to its clients' specific needs.

Precision's TumorGenesis subsidiary is developing a new rapid approach to growing tumors in the laboratory, which essentially "fools" cancer cells into thinking they are still growing inside a patient. Its proprietary Oncology Discovery Technology Platform kits will assist researchers and clinicians to identify which cancer cells bind to specific biomarkers.

Adaptimmune & Alpine Immune Sciences Announce Collaboration & License Agreement

Adaptimmune Therapeutics plc and Alpine Immune Sciences, Inc. recently announced a collaboration and license agreement to develop next-generation SPEAR T-cell products that incorporate Alpine's secreted and transmembrane immunomodulatory protein (termed SIP and TIP) technology. This collaboration will further enhance Adaptimmune's efforts to design and develop next-generation SPEAR T-cell therapies.

"SPEAR T-cell therapies have demonstrated clinical promise for the treatment of solid tumors. Based on knowledge emerging from translational research of resistance mechanisms, we will start our first next-gen clinical study with ADP-A2M4CD8 in the second half of 2019," said Rafael Amado, Adaptimmune's President of R&D. "We are very excited to begin this collaboration with Alpine, which complements our research on next-generation SPEAR T-cells. We believe that Alpine's platform technology could engage further rapid and flexible immunomodulatory mechanisms, which would enable the development of future next-generation SPEAR T-cells with enhanced anti-tumor potential."

"Our directed evolution platform has successfully generated many unique, multi-functional protein domains designed to favorably modulate the tumor microenvironment via validated immune targets," added Stanford Peng, MD PhD, Alpine's President and Head of Research & Development. "We look forward to working with Adaptimmune to develop next-generation SPEAR T-cell therapies to achieve improved clinical outcomes."

Alpine and Adaptimmune will collaborate on a specified number of programs to develop SIP and TIP candidates with tailored affinities and modulatory activities that may enhance the anti-tumor responses seen with Adaptimmune's SPEAR T-cells. For each program, Adaptimmune has an option to take a worldwide exclusive license for development and commercialization of SPEAR T-cell products incorporating the developed SIP or TIP candidate for the treatment of cancer.

Under the terms of the collaboration agreement, Adaptimmune will provide an upfront payment and research funding for ongoing programs. In addition, Alpine may be eligible for downstream development and commercialization milestones up to $288 million, if all pre-specified milestones for each program are achieved. Alpine will receive low-single digit royalties on worldwide net sales of the applicable products.

Adaptimmune is a clinical-stage biopharmaceutical company focused on the development of novel cancer immunotherapy products for cancer patients. The company's unique SPEAR (Specific Peptide Enhanced Affinity Receptor) T cell platform enables the engineering of T-cells to target and destroy cancer across multiple solid tumors.

Alpine Immune Sciences, Inc. is committed to leading a new wave of functional immune therapeutics. Alpine is employing directed evolution to create potentially powerful multifunctional immunotherapies to improve patients' lives. Alpine has two lead programs. The first, ALPN-101 for autoimmune/inflammatory diseases, is a dual ICOS/CD28 antagonist, engineered to reduce pathogenic immune responses. The second, ALPN-202 for cancer, is a dual PD-L1/CTLA-4 antagonist and PD-L1-dependent CD28 co-stimulator intended to combine checkpoint inhibition with T cell co-stimulation – an approach currently absent from approved checkpoint therapies. Alpine is backed by world-class research and development capabilities, a highly-productive scientific platform, and a proven management team.

ProBioGen & Vaccitech Sign License Agreement

ProBioGen AG and Vaccitech, Ltd. jointly announced signing a license agreement in which Vaccitech will gain access to ProBioGen's proprietary technology platform based on the AGE1.CR duck retina cell line for production of its viral vectored vaccines. Earlier work leading to the license confirmed that the AGE1.CR duck cell technology allows large-scale manufacturing with higher production yields and lower cost of goods compared to other poxvirus production technologies.

"We have developed the AGE1.CR designer cell line, the chemically defined media, and the process over many years, and have solved the main challenges for the production of highly attenuated poxvirus vectors. We are very pleased to see a strong industry demand for our platform and are convinced that Vaccitech's highly innovative vaccine approach will greatly benefit from it," ProBioGen's CSO, Dr. Volker Sandig.

"We are delighted to work with ProBioGen and manufacture our innovative, universal flu vaccine, VTP-100, on the novel AGE1.CR.pIX duck cell line. Both safety and immunogenicity profiles of VTP-100 manufactured on the AGE1.CR.pIX duck cell line are comparable to those manufactured on CEF, used in previous trials. These positive results support AGE1.CR.pIX-based manufacture of the vaccine for future clinical studies," added Vaccitech's CEO, Dr. Thomas G. Evans.

ProBioGen is a premier, Berlin-based specialist for developing and manufacturing complex therapeutic glycoproteins viral vectors and vaccine technologies. Combining both state-of-the-art protein and virus platforms, based on ProBioGen's CHO.RiGHT and AGE1.CR expression and manufacturing platforms, respectively, together with intelligent product-specific technologies, yield biologics with optimized properties.

Rapid and integrated cell line and process development, comprehensive analytical development, and following reliable GMP manufacturing is performed by a highly skilled and experienced team. All services and technologies are embedded in a total quality management system to assure compliance with international ISO and GMP standards (EMA/FDA).

Vaccitech is a spin-out of the University of Oxford and leader in the use of viral vectors to treat and prevent diseases that require CD8+ T cell induction, such as infectious diseases and some cancers. The company is developing products using its unique, proprietary vaccine technology platform, conceived at one of the most prestigious vaccine research institutes in the world, the Jenner Institute. The company is backed by investors that include Google Ventures, Sequoia China and Oxford Science Innovation.

Vaccitech is engaged in Phase II clinical programs for universal influenza and prostate cancer, Phase I for MERS, and preclinical programs for 5 other therapeutic infectious disease and oncology indications, including HPV and HBV infections.

Elligo Health Research Launches Novel IntElligo Research Stack Clinical Technology

Elligo Health Research recently announced the launch of its innovative IntElligo Research Stack clinical technology. This standards-based technology platform, which powers the System of Accelerated Research (SOAR) model, will be launched this month as the eSource documentation tool at Elligo's Research Ready network of study sites.

"IntElligo can be set up per the study protocol in hours and easily follows the workflow in any physician's office," said Jacylyn Bodmer, Elligo's Chief Information Officer. "We are improving data quality while relieving administrative burden at the research site and enabling more patient-centric interactions. IntElligo also facilitates remote monitoring, which results in faster source data verification and financial payments to our physicians."

"IntElligo bridges health care and research, leveraging global industry standards from the start (CDISC PRM and CDASH), thus facilitating aggregation and tabulation into CDISC SD, the required format for regulatory eSubmissions to the FDA and Japan's PMDA," added Rebecca Kush, PhD, Elligo's Chief Scientific Officer.

In addition, the technology provides real-time management financial management, reports, and analytics across research sites; saves time and preserves data integrity by eliminating transcription; and achieves true eSource. Furthermore, it creates the opportunity to transform research through the SOAR model — expanding patient access and driving efficiency by enabling direct data from source to submission.

"By uniting our Goes Direct approach with this technology and infrastructure to support physicians, we are creating the ultimate solution for clinical trial execution," said John Potthoff, PhD, Elligo CEO. "The IntElligo platform will become a primary resource for our study sites, increasing the ability for physicians to provide research as a care option and enabling more patients to benefit."

Elligo Health Research, an integrated research organization, accelerates the development of new pharmaceutical, biotechnology, medical device, and diagnostic products using our novel IntElligo Research Stack clinical technology and our Goes Direct approach. We unite the best clinical experts with the best research infrastructure — creating the ultimate clinical trial solution. By maintaining the integrity of the trusted patient and physician relationship and building global communities of research that leverage electronic health records, we ensure all patients have access to clinical trials as a care option. For more information, visit elligodirect.com.

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Octapharma Study Demonstrates Cutaquig Efficacy & Safety

Octapharma presented clinical research results at the Clinical Immunology Society Annual Meeting in Atlanta demonstrating the efficacy and safety of cutaquig [Immune Globulin Subcutaneous (Human) – hipp], a 16.5% immune globulin solution for subcutaneous infusion indicated for treatment of primary humoral immunodeficiency (PI) in adults.

"Subcutaneously administered immunoglobulin (SCIG) is increasingly used to treat patients with primary immunodeficiencies," said Octapharma USA President Flemming Nielsen. "In addition to not requiring venous access, SCIG has few systemic side effects and can help improve patient quality of life. The evaluation of adverse events and infusion site reactions during the study showed that subcutaneous administration of cutaquig was well tolerated and safe in the assessed patient population."

The clinical trial's primary endpoint of preventing serious bacterial infections (SBIs) was met as none of the patients experienced an SBI during the study. Based on historical data, an SBI rate of less than 1 per person a year provides substantial evidence of efficacy.

The study, titled Efficacy, Safety and Tolerability of a Subcutaneous Human Immunoglobulin 16.5% (cutaquig) in Adult Patients with Primary Immune Deficiencies, further reported a rate of other infections per person a year of 2.73 with 65% of the infections being mild and 35% moderate in intensity. Eighty-five percent of infusions had no site reactions.

"The patients were extremely thankful to be able to use the subcutaneous method of administration with cutaquig as this provided a safe method to do the infusions at home avoiding the long and often tedious travel to the hospital for treatment," said Dr. Elena Latysheva of the National Research Center Institute of Immunology FMBA in Moscow, Russia.

"This study corroborates the pivotal global cutaquig trial recently published in Frontiers in Immunology, where also none of the patients experienced a serious bacterial infection," said Dr. Roger H. Kobayashi, UCLA School of Medicine Clinical Professor, Division of Pediatric Allergy and Immunology.

Cutaquig (Immune Globulin Subcutaneous (Human) - hipp) is a 16.5% immune globulin solution for subcutaneous infusion indicated for treatment of primary humoral immunodeficiency (PI) in adults.

Thrombosis may occur with immune globulin products, including cutaquig. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.

For patients at risk of thrombosis, administer cutaquig at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk of hyperviscosity.

Headquartered in Lachen, Switzerland, Octapharma is one of the largest human protein products manufacturers in the world and has been committed to patient care and medical innovation since 1983. Its core business is the development and production of human proteins from human plasma and human cell lines.

Merus Announces First Patient Treated in Phase 1 Clinical Trial for Advanced Solid Tumors

Merus N.V. recently announced the first patient has been treated in its Phase 1 trial evaluating safety, tolerability, and preliminary efficacy of MCLA-145 for the treatment of patients with advanced solid tumors. MCLA-145 is a potential first-in-class PD-L1 x CD137 Biclonics being developed in collaboration with Incyte for the treatment of solid tumors.

"We are very pleased to announce the initiation of our Phase 1 trial for MCLA-145," said Andres Sirulnik, MD, PhD, Executive Vice President and Chief Medical Officer of Merus. "MCLA-145's unique triple action is designed to recruit T-cells, activate T-cells and also prevent T-cell exhaustion. Importantly, MCLA-145 has potential to overcome known systemic side effects of CD137 agonists currently in development through more targeted delivery to the tumor microenvironment, and to address a significant unmet need in patient populations not benefitting from current immunotherapeutic agents."

The Phase 1, open-label, single-agent clinical trial of MCLA-145 consists of dose escalation followed by dose expansion. Primary objectives of the Phase 1 trial are dose finding, evaluation of safety and tolerability of MCLA-145 in patients with advanced solid tumors. The Phase 1 trial will also examine potential preliminary antitumor activity and functional target engagement of single-agent MCLA-145. More details of the trial can be found at https://clinicaltrials.gov/ct2/show/NCT03922204.

Discovered through an unbiased functional screening of multiple immunomodulatory target combinations, MCLA-145 is a Biclonics T-cell agonist that also blocks T-cell inhibitor signals, and binds with high affinity and specificity to human PD-L1 and CD137 in preclinical models. The unique immunostimulatory profile of MCLA-145 derives from the ability to potently activate immune effector cells in the context of the tumor microenvironment while simultaneously blocking inhibitory signals in the same immune cell population.

Merus is developing MCLA-145 as part of a collaboration entered into with Incyte in December 2016 to potentially develop and commercialize up to 11 bispecific and monospecific antibodies from the Merus Biclonics platform. Under the terms of the collaboration, Merus will retain all rights to develop and commercialize MCLA-145, if approved, in the US, while Incyte has rights to develop and commercialize MCLA-145, if approved, outside the US.

Merus is a clinical-stage immuno-oncology company developing innovative full-length human bispecific antibody therapeutics, referred to as Biclonics. Biclonics, which are based on the full-length IgG format, are manufactured using industry standard processes and have been observed in preclinical and clinical studies to have several of the same features of conventional human monoclonal antibodies, such as long half-life and low immunogenicity. For more information, visit www.merus.nl.

Sarepta Announces Agreement With Nationwide Children's Hospital for Rights to its Gene Therapy Program

Sarepta Therapeutics, Inc. recently announced it has recently signed an agreement with the Research Institute at Nationwide Children's Hospital (Nationwide Children's) giving Sarepta the exclusive option to a Nationwide Children's gene therapy candidate, calpain 3 (CAPN-3), to treat Limb-girdle muscular dystrophy type 2A (LGMD2A).

LGMDs represent a group of distinct genetic neuromuscular diseases with a generally common set of symptoms, including progressive, debilitating weakness, and wasting that begins in muscles around the hips and shoulders before progressing to muscles in the arms and legs. Many LGMD sub-types are seriously life-limiting and often life-ending diseases. Also known as calpainopathy, LGMD2A is caused by mutations in the CAPN-3 gene and is the most common type of LGMD, accounting for almost a third of cases.

Like Sarepta's micro-dystrophin and five other LGMD programs, the LGMD2A program employs the AAVrh74 vector, designed to systematically and robustly deliver treatment to skeletal muscle, including the diaphragm, without promiscuously crossing the blood brain barrier, making it an ideal candidate to treat muscle disease.

The CAPN-3 program is currently in pre-clinical trials. The program is led by Zarife Sahenk, MD, PhD, an attending neurologist at Nationwide Children's, Director of Clinical and Experimental Neuromuscular Pathology at The Research Institute at Nationwide Children's and Professor of Pediatrics, Pathology and Neurology at The Ohio State University College of Medicine.

"We are pleased to expand and deepen our working relationship with Nationwide Children's and Dr. Sahenk, with whom we are already working on a gene therapy candidate to treat Charcot-Marie-Tooth. With six LGMD gene therapy programs now in our portfolio, our commitment and investment in research for this group of neuromuscular diseases is unparalleled," said Doug Ingram, Sarepta's President and Chief Executive Officer. "Recent positive early results from our LGMD2E program support expanding our development strategy to LGMD2A, as both programs utilize AAVrh74 vector, address sub-populations of LGMD, and address a well-characterized disease by directly replacing the missing protein which is the cause of the disease by transducing the native protein. We continue to fuel our gene therapy development engine aimed at building an enduring model that delivers potentially transformative therapies to treat genetically based diseases."

"LGMD2A is the most common form of limb-girdle muscular dystrophy and its relentless progression causes patients to lose the ability to walk in early adulthood," said Dr. Zahenk. "Our preclinical work suggests that a gene therapy approach has the potential to help those living with LGMD2A and we look forward to collaborating with Sarepta to advance this program in the clinic."

Limb-girdle muscular dystrophies are genetic diseases that cause progressive, debilitating weakness and wasting that begins in muscles around the hips and shoulders before progressing to muscles in the arms and legs. Sarepta's six LGMD gene therapy programs in development now include LGMD2E, LGMD2D, LGMD2C, LGMD2B, LGMD2L and LGMD2A.

FORMULATION FORUM

Amorphous Formulations for Insoluble Drugs: Rational Design & Practical Approaches on Formulation Screening & Development

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

Jim Huang, PhD
Founder & CEO
Ascendia Pharmaceuticals
j.huang@ascendiapharma.com

For poorly water-soluble "brick dust compounds" (Classes II and IV) characterized as high molecular weights, large log P values, and poor water solubilities, the drug absorptions process is often limited by the drug solubility or dissolution rate from the dosage forms. The bioavailability and absorption rate of those compounds into human body can be significantly improved by: 1) an increase in effective dissolution surface area by particle size reduction to the micron or the nanometer size range or by increasing wettability of the hydrophobic drugs, and 2) improvement in the solubility by formation of amorphous nanoparticles or amorphous solid dispersions that form nanoparticles in situ in the GI fluids. However, a comprehensive understanding of amorphous properties and their relationship with *in vivo* performance are still lagging. Development of characterization techniques to elucidate the structure of amorphous materials, prediction of in vitro and in vivo performance, and custom design of amorphous formulations has remained as the three major needs for the development of an amorphous drug delivery system. The issues associated with amorphous formulations include solid state stability, chemical stability, reproducibility of API manufacturing, impurity of API, stability in aqueous solution, *in vitro in vivo* performance, process and scale-up, etc.

AMORPHOUS DRUG DELIVERY SYSTEMS

Amorphous API

If the amorphous API can be reproducibly manufactured, and it possesses characteristics that could maintain its physical-chemical properties during process, storage, and in vivo physiological conditions, eg, a high transition point, (Tg-Tstorage > 50°C), strong glass former, non-hygroscopicity, and ability to maintain supersaturation in GI fluid within the transition time period without recrystallization, the amorphous API could be directly incorporated into the dosage forms by traditional formulation technologies and maintain its stability within the product shelf-life. For example, Crestor® (rosuvastatin calcium) tablets marketed by AstraZeneca contain amorphous API that is stable during manufacturing and storage conditions.

Amorphous Solid Dispersion

However, because most low-molecular-weight pharmaceutical APIs form a fragile glass, which has a Tg of < 75°C, and readily recrystallize out during storage or *in vivo* dissolution, it is often necessary to utilize excipients, eg, polymer or surfactant, to form a multiple-component amorphous system (ie, amorphous solid dispersion) in order to stabilize and inhibit the amorphous drug from

crystallization at its solid or aqueous states. The introduction of stabilizing agents into the multiple-component amorphous system would not only optimize the stability of the amorphous drugs, but also improve the *in vivo* functionality and handling of the amorphous dosage form, eg, a reduction in stickiness, powder flow properties, moisture scavenging and protection, requirement in storage conditions, and packaging, etc.

Amorphous Nanoparticles

Amorphous nanoparticles are a combination of nanosizing and amorphous dispersion formation that theoretically could achieve the maximum enhancement in solubility and dissolution rate. It typically contains drug and polymers, surfactants, carriers, and other stabilizer(s). Amorphous drug nanoparticles can be prepared by a bottom-up process, high-shear mixing, high-pressure homogenization, or combination of a bottom-up process with a nanosizing process. Drug is dissolved in organic solvent(s) together with other stabilizer excipients, which is induced to precipitate out by introduction of non-solvent(s). Variation of formulation and process parameters can generate amorphous drug nanoparticles of different sizes that can be further incorporated into dosage forms by a downstream process.

RATIONAL DESIGN OF AMORPHOUS FORMULATION

To take advantage of the higher solubility of amorphous solids and to mitigate risks associated with physical instability, an understanding of molecular structure of amorphous materials and their relationship with the physical-chemical properties is essential for development of stable amorphous dosage forms. Two of the physical properties that are especially important to physical stability of amorphous solid dispersions are the drug-polymer miscibility and the solid solubility of the drug in polymeric matrices. Miscibility refers to capability of mixing two liquids in any ratio without separation of two phases, while solubility is defined as "the spontaneous interaction of two or more substances to form a homogenous molecular dispersion."[1] An understanding of these two properties will help in selecting an appropriate polymer and surfactant and determining an optimal amorphous drug-loading level for rational design of a stable amorphous solid dispersion formulation.

Drug-Polymer Miscibility

The extent of interaction between drug and polymer (interaction parameter, $X_{1,2}$) is defined as the difference in solubility parameter between solute and solvent. See equation 1.

$$\chi_{1,2} = \frac{(\delta_1 - \delta_2)^2 V_2}{RT}$$

Equation 1

According to a miscibility study conducted by Greenhalgh et al on molten drugs and excipients possessing various solubility parameters, there is a trend in terms of increasing the degree of immiscibility with increasing the difference in the solubility parameter between drug and carrier.[2] The difference in solubility parameters could give an indication of the potential miscibility between the drug and the polymer in solid dispersions (Table 1). One of the methods for determination of drug-polymer interaction parameter is melting-point depression method as described by Taylor et al.[3]

Drug Solid Solubility in Polymer

Due to the lengthy time period required to achieve equilibrium due to the glassy nature of most pharmaceutical solid dispersion systems, it is often challenging to determine the equilibrium of drug solid solubility in a polymer. For practical reasons, the pharmaceutical industry commonly determines the kinetic solid solubility of drug within a polymer using X-ray powder diffractometry (XRPD) and thermal analysis methods. Other qualitative techniques, such as Hot-stage microscopy, scanning electron microscopy (SEM), Raman spectroscopy, Fourier-transform infrared (FTIR) spectroscopy, solid-state nuclear magnetic resonance (SSNMR) spectroscopy, etc, are normally used to confirm the physical

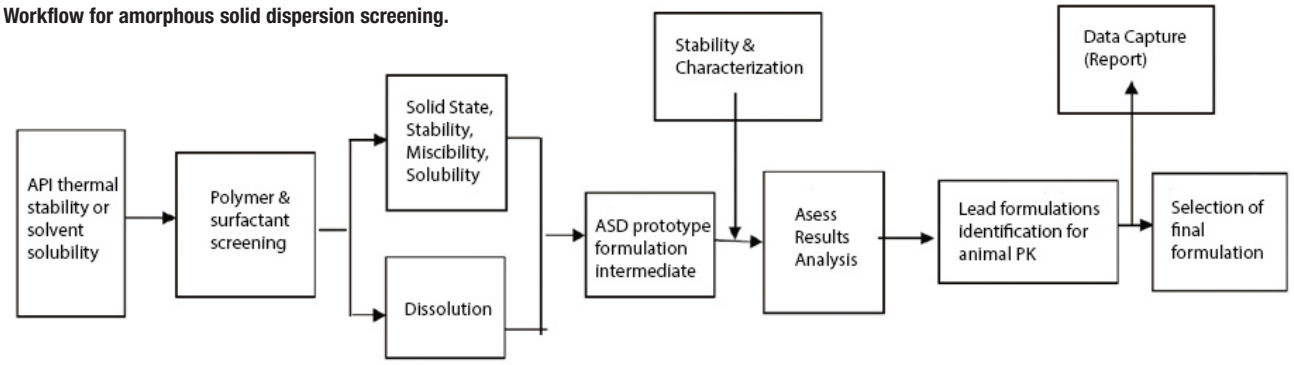
TABLE 1

Difference in solubility parameter between drug and carrier	Likelihood of Miscibility
<7.5	Likely complete miscible
7.4-15.0	Likely partial miscible
>15.9	Likely total immiscible

Effect of Interaction Parameter With Drug-Polymer Miscibility

FIGURE 1

Workflow for amorphous solid dispersion screening.



state observed by XRPD and differential scanning calorimetry (DSC).

AMORPHOUS FORMULATION SCREENING & IN VITRO EVALUATION

The primary goals of a screening study are to find a formulation of polymer and/or surfactant that is physically miscible and chemically compatible with drug, can load a reasonable amount of drug in a matrix, and enhance solubility and absorption of compound *in vitro* and *in vivo*. For a screening study, a solvent evaporation method can be utilized in combination with a miniature design that minimizes the amount of compound usage while allowing for screening enough quantity of formula by a DOE design. Samples can be prepared using 96-well plate, bottles, or vials with a flash drying of solvent under vacuum, heat, and/or inner gas. Potential lead formulations can then be optimized and manufactured on a larger scale for testing, including physical and chemical stability studies, in vitro release characterization, and in vitro studies in animals. Excipients can be selected from HPMC, PVP, PVPVA, PEG, HPC, Kollicoat IR, polymethyl acrylate, HPMCAS, Poloxamer, SoluPlus, hydropropyl methylcellulose phthalate, Cyclodextrin, Polysorbate, TPGS, AOT, SLS, Gelucire 44/14, etc, for screening of drug-polymer miscibility, stability, solubility, and dissolution.

A typical workflow for amorphous solid dispersion screening consists of the following elements:

- API thermal stability tests or solvent solubility
- Polymer/surfactant screening by drug-polymer miscibility, solid solubility, dissolution, and stressed stability
- Identification of prototype formulations and scale-up
- Characterization of prototype formulations by assay/related substance, polarized microscopy, KF, GC, DSC, SEM, XRPD, and in vitro dissolution using conditions simulating GI transition from gastric to intestine
- Animal PK study of prototype formulations, and feedback to formulation optimization based on animal study results
- Short-term stability testing at various temperature and humidity conditions to predict long-term shelf-life
- Lead formulation recommendation and data capture with a report

PROCESS TECHNOLOGY SELECTION

Selection of process technology for amorphous formulation depends on the compound properties. For example, API melting point, thermal stability, and solvent solubility will determine the processability of drug compound either by hot-melt extrusion (HME) or spray-drying process. Table 2 lists examples of commercial products and process technology utilized. Due to kinetic nature of amorphous materials, the performance of amorphous formulation will be affected by the selected technology and the process parameters.

Spray-drying is a well-established and widely used process for transforming formulation in liquid solutions or suspensions into dry powdered forms that is suitable for heat-sensitive compounds. Phase separation of drug and polymer could be prevented by rapid removal of solvent from the droplets of the spray solution and thereby rapid solidification of the droplets. HME has advantages in a simple continuous process with fewer manufacturing steps that could be useful for low-melting compounds with low-solvent solubility.

Liquid filling technologies for direct encapsulation of melt solid dispersions into hard capsules has gained popularity. The

TABLE 2

Brand Name (Manufacturer)	Generic Name	Manufacturing Method	Main Excipients
Gris-PEG (Wander)	Griseofulvin–PEG	melting method	PEG
Cesamet: (Valeant Pharm & Lilly)	Nabilone-PVP	solvent granulation	PVP
Rezulin: (Parke-Davis, withdrawn due to tox issue)	Troglitazone-PVP	melt-extruded	PVP
Kaletra: copolymer (Abbott)	lopinavir & Ritonavir in PVP/VA	melt-extruded	PVP/VA
Isoptin SRE	Verapamil sustained release	melt-extrusion	
Ibuprofen	Fast action formulation	melt-extrusion	
Sporanox: 1) (Janssen Pharm)	Itraconazole with hypromellose	hot-melt extrusion	HPMC
Sporanox: 2) (Janssen Pharm)	Itraconazole in hypromellose	drug layered in sugar spheres	HPMC
Intelence: (Tibotec)	Etravirine with hypromellose & microcrystalline cellulose	spray-dried	HPMC

Examples of Marketed Amorphous Formulations & Process Technology

manufacturing of this amorphous dosage form involves the dissolving of drugs in melted carriers and the filling of the solutions into hard gelatin capsules. Lipid-based solid dispersion systems developed by this technology have been used in drug discovery and development.

DOSAGE FORM DEVELOPMENT AT DIFFERENT STAGES OF DEVELOPMENT

For preclinical studies or early phase clinical studies, aqueous suspensions of amorphous formulations after reconstitution are ideal for dosing for DMPK and toxicological evaluation. Studies should be done to ensure that amorphous formulations will not crystallize out in the aqueous suspension during the study period. Optimization in drug loading and polymer/surfactant level to inhibit compound crystallization may need to be undertaken to overcome the issue.

Powder in hard gelatin capsules is preferred for larger animals and early phase human trials, which has longer term stability than the reconstituted aqueous suspension. However, gelling may frequently occur inside the capsules during dissolution that may compromise the drug performance in vivo.

Tablets are the most preferred dosage form for late-stage and commercialization of amorphous materials. Spray dried amorphous powders will require secondary drying to remove the residual solvent and dry granulation by roller compaction to increase density. Amorphous formulation intermediates made by spray drying after dry granulation, HME, or solvent-evaporation processes requires milling to optimize the granule particle size distribution prior to further processing to ensure in vivo dissolution performance, flowability, and tabletability. Amorphous tablet formulation typically requires additional super-disintegrants, fillers, lubricants, and glidants in order to ensure manufacturability and rapid disintegration of the tablets. In addition, effects of excipient's moisture level and hygroscopicity, and compression force on the amorphous stability will need to be evaluated. ◆

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2018 Global Drug Delivery & Formulation REPORT

Four of a Four-Part Series

Part 1: A Global Review of 2018 Product Approvals

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

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

Part 4: The Drug Delivery and Formulation Pipeline

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

Introduction

Understanding the pharmaceutical pipeline from the perspective of drug delivery and formulation is tricky. Once you start looking too far into the earlier stage pipeline, you find yourself dealing with incomplete and often undisclosed information. Many of these earlier development products, especially Phase 1 and earlier, are "moonshots" of sorts in which companies are pushing the boundaries of experience in hopes of a breakthrough. For these reasons among others, the pipeline portion of this 2018 Global Drug Delivery & Formulation Report is restricted to products in either Phase 3 or Registration stages of development. These products generally have disclosed indication targets and administration routes, but in some cases, lack details regarding dosage form and formulation.

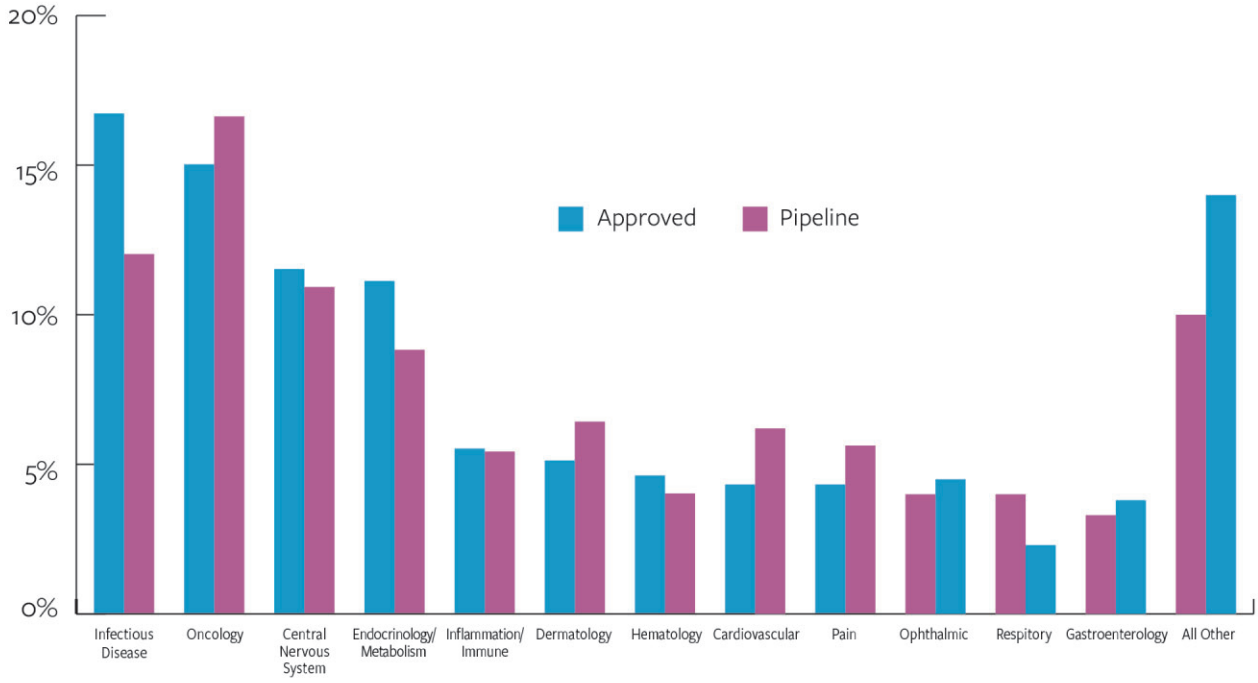
This review compares current Phase 3 and Registration-stage products with products first approved since 2014 in the United States, Japan, or Europe.

The net/net of this analysis, presented over the following pages, reveals more consistency than change in the pipeline products. There are more Oncology products in later stage development, generally targeted antibodies, proteins, and small molecules. This is offset by a drop in the proportion of Infectious Disease agents in development.

The increase emphasis on Oncology and other specific molecular mechanism-targeted therapeutics, often with macromolecules, has resulted in a shift to more Injection-based therapeutics. In terms of molecule types in the pipeline, there is little or no change seen in the ratio of small molecule to macromolecule therapeutics. But among the macromolecules in development, there appears to be an increased proportion of Peptides, was well Gene and Cell Therapy products, at the apparent expense of Protein and Antibody therapeutics.

Oncology is the Leading Indication in the Late-Stage Pipeline

Chart 1: Approved & Product Pipeline by Indication (Top 12)



Source: PharmaCircle Pipeline & Products Intelligence module

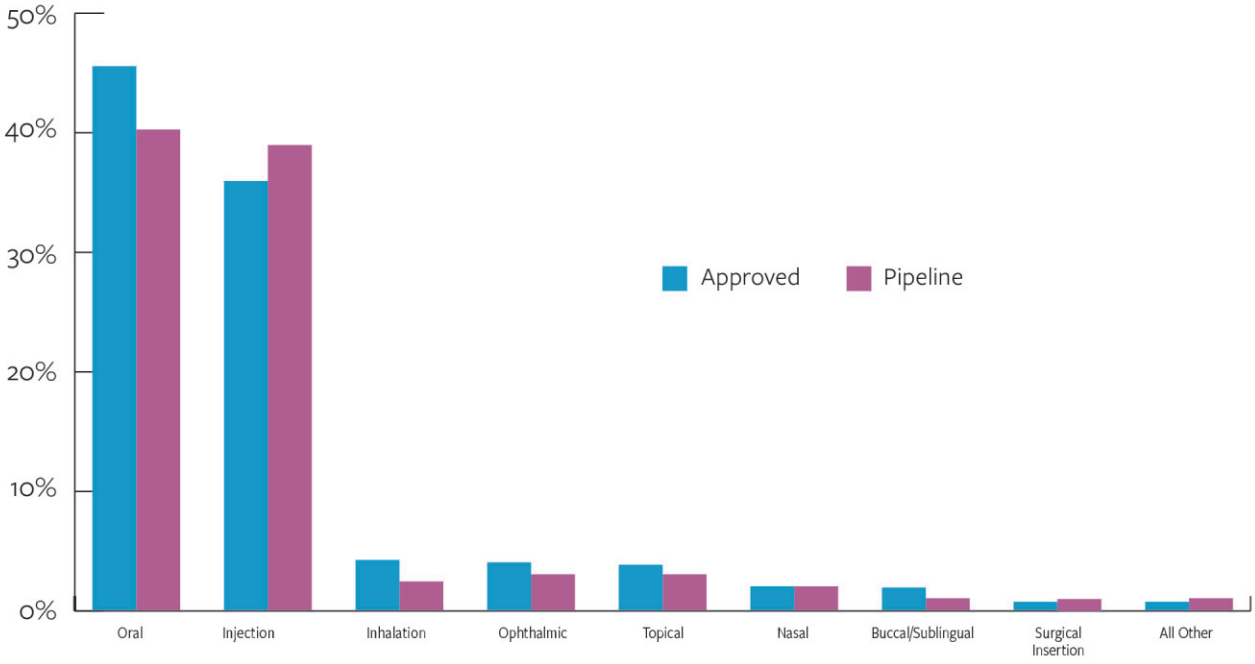
Notes:

1. Approved refers to products with first approvals between 2014 and March 2019 in the US, Europe, or Japan. Generics and Biosimilars are not included. (N=683)
2. Pipeline refers to products identified in Phase 3 or Registration stages of development in major markets as of March 2019. Generics and Biosimilars are not included. (N=1,380)
3. All Other includes Musculoskeletal, Genetic, Genitourinary, Anesthesia, and Men's and Women's Health indications. Each of which represented less than 3% of the total.

- Oncology has moved to the number one development indication, accounting for almost 17% of the late-stage pharmaceutical pipeline.
- The relative drop of the Infectious Disease pipeline is a reflection of a shift away from HIV and HCV after a remarkable string of approvals in the past decade.
- The Cardiovascular market is seeing an increase on the basis of novel therapeutics for more poorly managed conditions, such as Pulmonary Arterial Hypertension.
- The uptick in the Pain sector is not associated with opioids, but rather proprietary formulations of non-opioids as well as novel analgesics.
- The Dermatology pipeline uptick includes a number of new formulations of established actives as well as new systemic products.
- Following a flurry of new Respiratory product approvals related to novel devices, the pipeline has shrunk in relative terms.

The Oral Route is Maintaining a Slim Lead Over Injection in the Late-Stage Pipeline

Chart 2: Approved & Product Pipeline by Route (Top 8)



Source: PharmaCircle Pipeline & Products Intelligence module

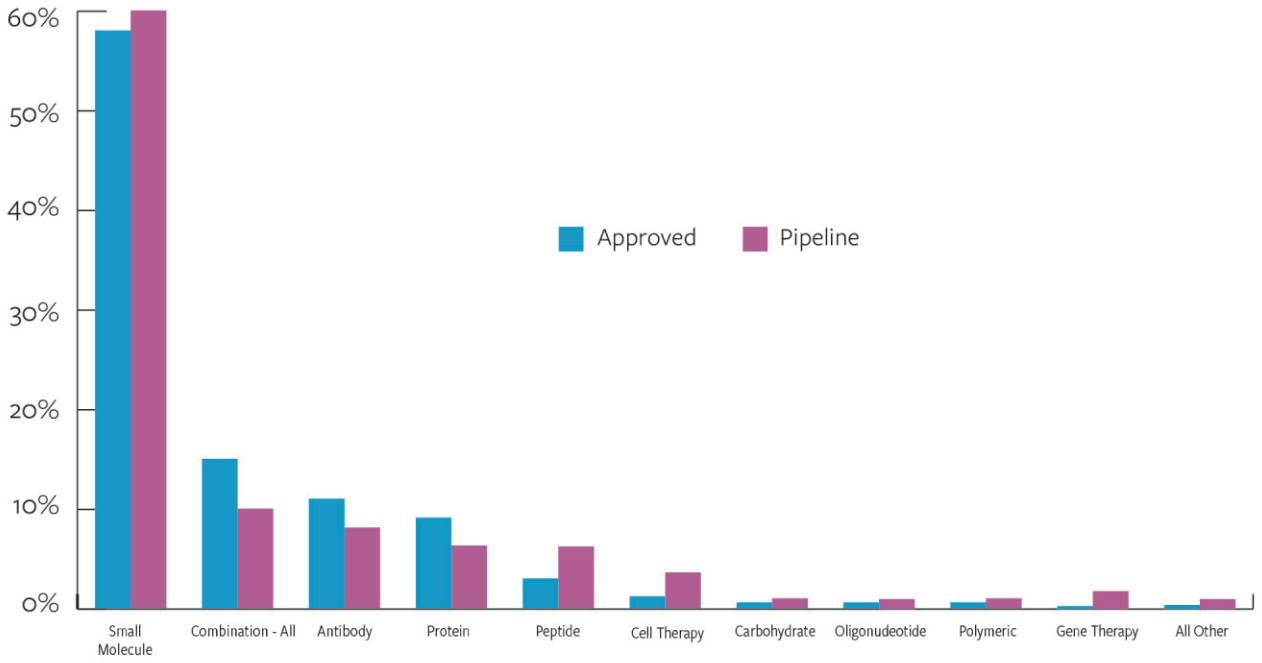
Notes:

1. Approved refers to products with first approvals between 2014 and March 2019 in either the US, Europe, or Japan. Generics and Biosimilars are not included. (N=693)
2. Pipeline refers to products identified in Phase 3 or Registration stages of development in major markets as of March 2019. Generics and Biosimilars are not included. (N=1,380)
3. All Other includes products delivered by the Otic, Vaginal, Transdermal, or Rectal routes

- The relative drop in the Oral Route seen with the Pipeline products is not surprising in light of an expanded Oncology pipeline largely dependent on parenteral administration.
- The drop in the Inhalation Route pipeline is consistent with the drop in the number of products targeted to Respiratory indications.
- The increase in Topical Route pipeline products parallels the increase in products targeted to Dermatology indications.
- The Buccal and Sublingual routes of administration continue to see little activity in terms of the late-stage pipeline in part a consequence of the relatively poor commercial success of earlier products.
- Transdermal route products, included in All Other, have seen little development interest in terms of the pipeline or recently approved products.
- Nasal delivery continues to see little activity, although newer devices and the potential success of Janssen's Spravato may spur future investments.

Small Molecule Therapeutics Continue to Dominate the Late-Stage Development Pipeline

Chart 3: Approved & Product Pipeline by Molecule Type (Top 10)



Source: PharmaCircle Pipeline & Products Intelligence module

Notes:

1. Approved refers to products with first approvals between 2014 and March 2019 in either the US, Europe, or Japan. Generics and Biosimilars are not included. (N=693)
2. Pipeline refers to products identified in Phase 3 or Registration stages of development in major markets as of March 2019. Generics and Biosimilars are not included. Not all development-stage products have disclosed molecule types, which may impact this analysis. (N=1,247)
3. All Other includes a mix of Plasma-derived, RNA, Stem Cell, and Microbiome products, each with less than a half dozen identified products.

- Small Molecule therapeutics continues to account for more than half of all recently approved and late-stage pipeline products.
- The relative drop in Pipeline antibody products may simply reflect the 10% of Pipeline products that do not have a disclosed molecule type (see Note 2).
- Gene and Cell Therapy products in the late-stage pipeline account for 5.5% of all products, a remarkable leap from 1.5% in the recently approved products.
- The increase in Peptide-based therapeutics from 3% to 6% seems to represent a real trend in terms of the development pipeline.
- The drop in Fixed Dose Combination products is associated with relatively fewer Small Molecule products with two actives.
- Protein-based products showed a bit of a drop in the late-stage pipeline and may be a reflection of incomplete information on these development products (see Note 2).

Oral & Injection Dosage Forms Differ Little Between Approved & Pipeline Products

Chart 4: Approved & Oral Product Pipeline by Dosage Form (Top 4)

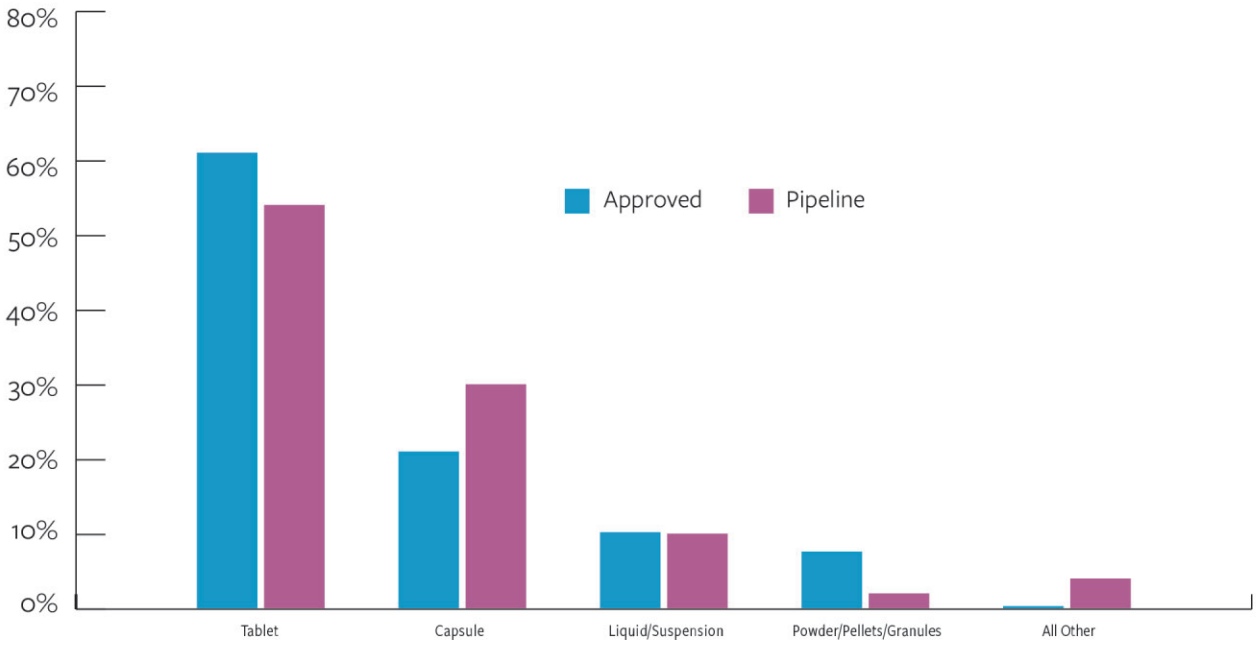
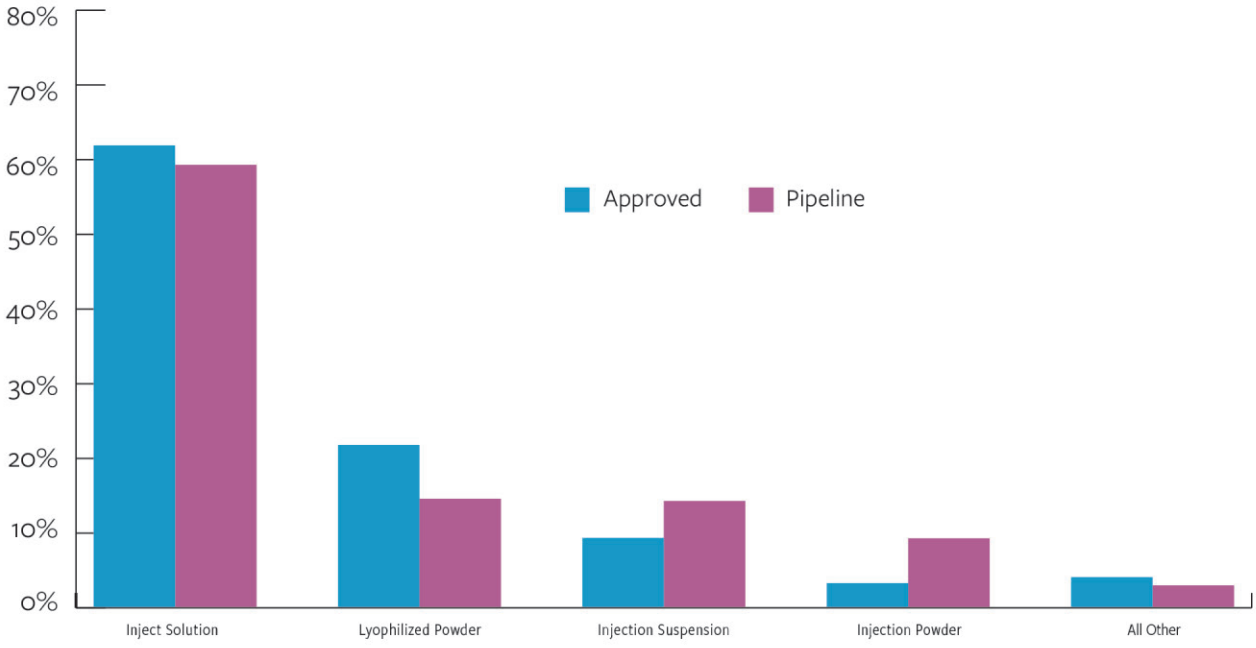


Chart 5: Approved & Injection Product Pipeline by Dosage Form (Top 4)



Source: PharmaCircle Pipeline & Products Intelligence module (both cahrts)

Notes:

1. See earlier charts for definitions of Approved and Pipeline.
2. Oral Approved (N=315). Oral Pipeline (N=499). Injection Approved (N=249). Injection Pipeline (N=380). In many cases, the Pipeline products have undisclosed Dosage Forms.

The Oral & Injection Pipelines Show Consistent Indication Changes

Chart 6: Approved & Oral Product Pipeline by Indication (Top 12)

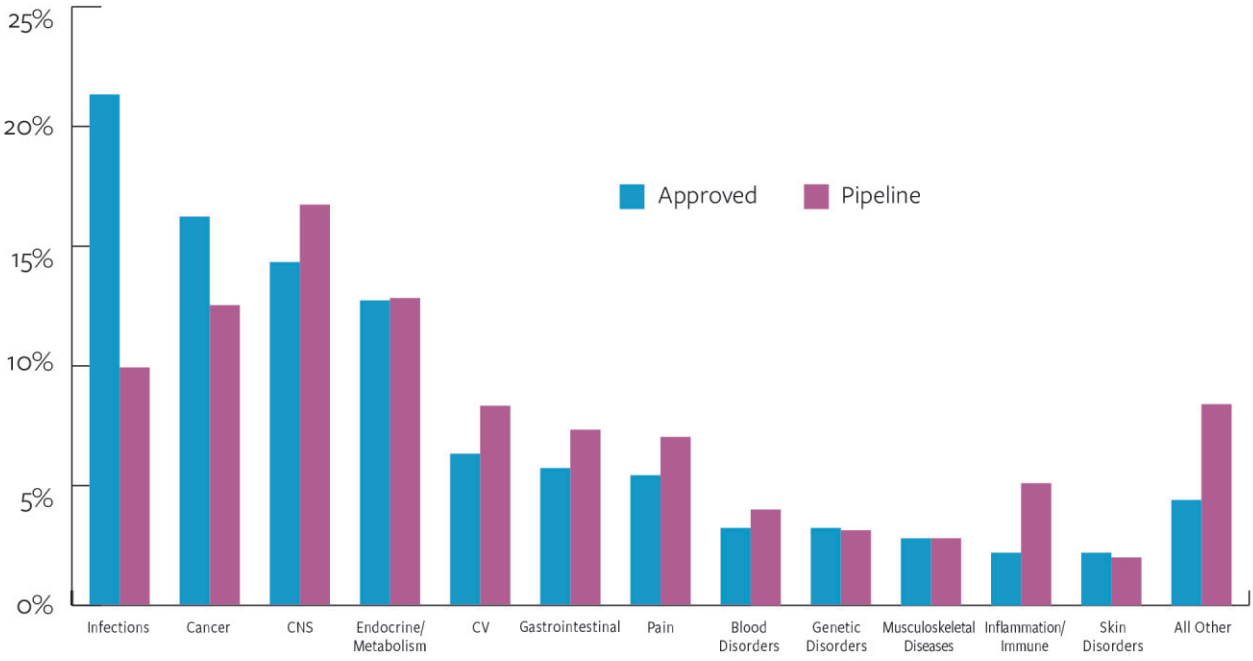
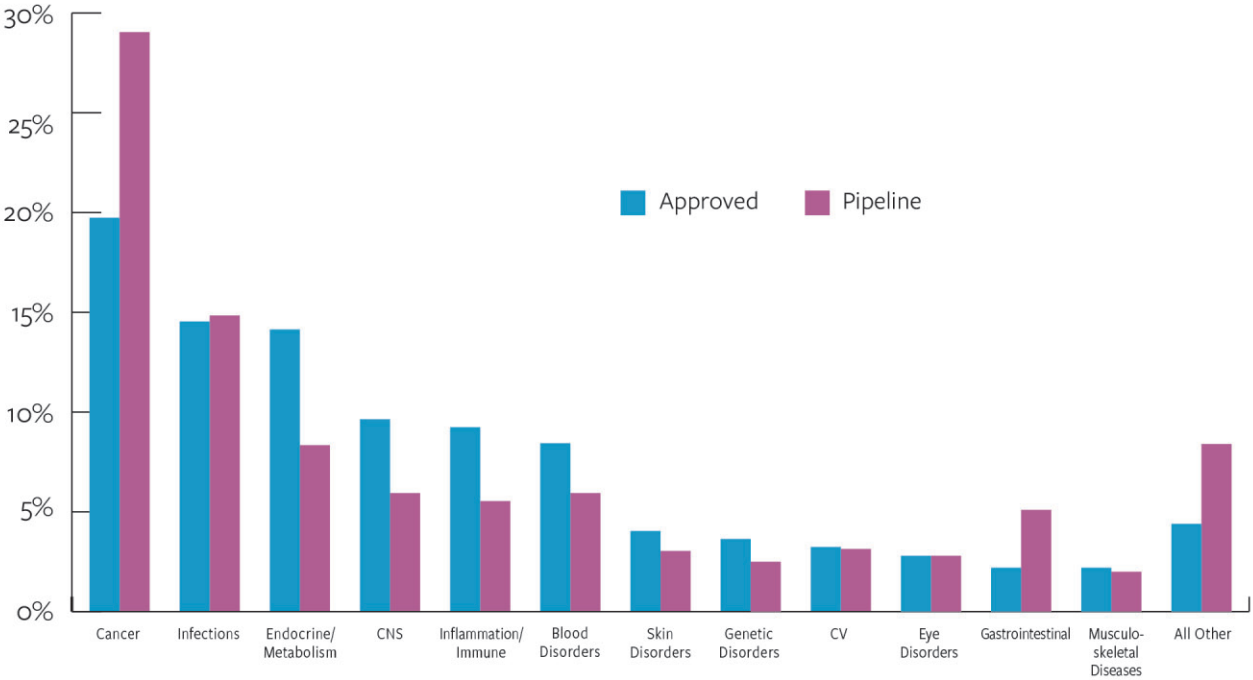


Chart 7: Approved & Injection Product Pipeline by Indication (Top 12)



Source: PharmaCircle Pipeline & Products Intelligence module (both charts)

Notes:

1. See earlier charts for definitions of Approved and Pipeline.
2. Oral Approved (N=315). Oral Pipeline (N=545). Injection Approved (N=249). Injection Pipeline (N=527). In many cases, the Pipeline products have undisclosed Dosage Forms.

Final Thoughts

Looking back at 2018, it's hard to find inflection points in the drug delivery and formulation sector. Looking forward, the late-stage pipeline suggests the future promises more of the same. Should that really be much of a surprise or concern? Do consumer electronics look that much different in 2019 than they did 5 years ago despite much shorter development cycles?

Breakthroughs are needed, and they will arrive. Novo Nordisk's filing earlier this year for approval of an oral formulation of semaglutide, its 4 kDa peptide, using the Emisphere Eligen technology is an important start. The Novo Nordisk filing suggests that oral delivery of larger peptides is effective and safe, although it seems oral dosing requires about 100 times the injectable dose. There is certainly room for improvement. How quickly will 100x be reduced to 20x or even 5x? What's most important is that proof principle has been established. It's no longer a question of whether it can be done, it has become a question of how much better can it become.

The past year experienced more variations on familiar drug delivery and formulation themes; variations on how the technology is deployed, the therapeutic target, and even the therapeutic strategy. In 2018, we saw a number of products approved using quite different PEGylation strategies, multiple smaller PEG units, a single large PEG, and a few mid-size PEG units. They all met different therapeutic objectives for different indications and different molecule types. And the dosing paradigm for ADHD was flipped by 12 hours with the approval of Jornay PM, with an evening dosing using a delayed-release formulation. Familiar but different.

Perhaps the most exciting development was provided by the growing pipeline of gene and cell therapy products that not only address therapeutic challenges with new molecular strategies, but can act as long-term in vivo therapeutic factories. How will drug delivery and formulation contribute? The selective delivery of CRISPR to targeted organs is a real challenge if it is to be used safely for somatic cell applications. Will drug formulators need to take tours of duty through bioengineering departments to expand their skill sets?

The merging of formulation with devices is seeing improved efficacy, safety, and convenience that lead to better healthcare outcomes. When can we expect to see development of the fabled Hypospray from Star Trek, a needleless delivery device with swappable medication vials?

Appreciate 2018 for what it was, another strong step forward for drug delivery and formulation on the path to improved patient outcomes. Inflection points are tricky to recognize, perhaps there were one or more in 2018 that will only be obvious years from now.

About the Authors

Tugrul T. Kararli, President & Founder, PharmaCircle LLC

Dr. Kararli earned his PhD in Pharmacology from the University of Florida in 1984 and his MBA from DePaul University in 1999. He worked at Searle/Pharmacia for 18 years with responsibilities in pharmaceutics, product development, drug delivery, and life cycle management. Dr. Kararli founded PharmaCircle in 2003 as a knowledge management organization serving top 20 pharmaceutical companies as well as numerous commercial and emerging-stage life sciences companies and suppliers across the globe. Dr. Kararli has authored numerous research articles on various aspects of pharmaceutics and drug delivery and holds more than a dozen US and international patents.

Kurt Sedo, Vice President of Operations, PharmaCircle LLC

Kurt Sedo earned his BS in Chemistry and Mathematics from the University of Wisconsin Stevens Point. Prior to joining PharmaCircle in 2003, he held various R&D Scientist positions within Searle/Pharmacia's Pharmaceutical Sciences Department in Analytical Development and Drug Delivery. Mr. Sedo's responsibilities with PharmaCircle include oversight of data integrity, project management, and customer service. In addition to authoring articles, Mr. Sedo regularly presents overviews of the state of drug delivery and formulation at industry conferences.

PARENTERAL DEVELOPMENT

Considerations in Developing Complex Parenteral Formulations

By: Iain MacGilp, PhD

INTRODUCTION

Parenteral formulations are broadly characterized as sterile solutions, suspensions, emulsions, and powders for reconstitution for injection or infusion; they are administered directly to subjects, entering the systemic circulation and typically providing rapid onset of action in comparison to orally administered products. Small-volume parenteral products are generally presented in vials or ready-to-use pre-filled syringes, providing ease-of-use in the clinical setting or for patient self-administration. The path to delivering these stable, apparently simple solution, suspension, or emulsion formulations is multi-faceted and requires a constant focus on key control measures through pre-formulation development to commercialization.

Formulation scientists, analytical chemists, process operations staff, and engineers collaborate with microbiologists, quality assurance colleagues, regulatory specialists, and clinicians to ensure each product meets target attributes for safe administration to patients. For a given product, target attributes are described in the product specification and for all parenteral products, this includes an absolute requirement to be sterile and pyrogen controlled. The management of input materials, fluid pathway, and the specific product formulation process all must be controlled to ensure these key attributes.

DEFINING COMPLEXITY

As the sterile injectable market continues to see rapid growth (~10% to 15% per annum) - outpacing growth of oral products - it is natural to see the diversity of parenteral product formulations increasing in parallel. Simple, stable aqueous solutions manufactured via aseptic filtration and filling or terminal sterilization remain the target of any sterile injectable development and many small molecule products continue to employ traditional solubilization techniques, including ionization (pH) adjustment and the use of cosolvents, surfactants, or complexing agents, such as cyclodextrins.

The definition of complexity in parenteral formulation development is broad; it varies based on the stage of development and the specific nature of the challenge. A notionally simple, stable reproducible laboratory formulation may carry a level of complexity in aseptic control if routine means of sterilization are unavailable.

Lyophilization, whilst a commonplace means to stabilize products (small molecules through peptides, proteins, antibodies, antibody drug conjugates), requires skilled formulators and a clear understanding of variables impacting scale-up to ensure smooth, ensured transition through clinical phase, scale-up, and commercialization. If the product can be manufactured using an embedded, qualified aseptic filtration process or can be supported better by terminal sterilization, the level of complexity is reduced for the aseptic manufacturing team.

However, a scenario with a lyophilized PLGA-loaded suspension product that cannot be supported by aseptic filtration nor ter-

"However, a scenario with a lyophilized PLGA-loaded suspension product that cannot be supported by aseptic filtration nor terminal sterilization can bring challenges to all teams involved in the product development. For the formulation scientist, drug loading, particle size control, ease/reliability of suspension, agglomeration, fill accuracy, and content uniformity all bring a level of challenge."

minal sterilization can bring challenges to all teams involved in the product development. For the formulation scientist, drug loading, particle size control, ease/reliability of suspension, agglomeration, fill accuracy, and content uniformity all bring a level of challenge. For the aseptic manufacturing team, the challenge (and thus the complexity) is additive; a specific aseptic process would need to be designed and likely requires specific media fill qualification to ensure process robustness.

PROCESS TECHNOLOGIES SUPPORTING COMPLEX PRODUCT GROWTH

A focus on the patient who will undoubtedly benefit through administration of a controlled, targeted-release product with reduced systemic exposure must be maintained. This remains a strong driver for processes to adapt to emerging technologies and critical clinical applications. Historically, cytotoxic or potent compounds may have been developed as "simple" formulations, offering little discrimination in the targeting of delivered dose to intended site of action. New formulation capabilities and/or delivery technologies are supporting the repurposing of established agents as targeted therapies or enabling the development of new, potent, chemical entity products as more focused products, maximizing efficacy whilst minimizing systemic risk.

An increased requirement to handle potent active substances has been an ongoing trend, and suitable containment requirements for these compounds, particularly in multi-product facilities, has been a focus for pharma companies and CDMOs alike. This focus has been matched by the growth of single-use technologies that seek to minimize risk of product cross contamination in multi-use facilities.

Single-use technologies also allow a modular approach in which complex fluid pathways can be designed as closed systems with sterile connectors. The ability to design a bespoke irradiated fluid pathway that can be assembled in a cleanroom greatly assists the transition of complex processes from laboratory to cleanroom.

Increased automation removes operators from the aseptic core and barrier systems, which effectively remove the operator from the aseptic process and is highly advantageous in reducing risk in the cGMP manufacture of complex formulations.

Differentiated filling technologies within Restricted Access Barrier Systems (RABS) or isolators may be necessary to support a broad range of formulation possibilities. Peristaltic pump processes are well suited to biologics, such as proteins and antibodies, in which sensitivity to shear is a concern. Peristaltic processes easily align with single-use technologies and rapid turnaround, reducing the requirement for product-specific cleaning and in turn allowing greater utilization of cleanroom facilities. Highly viscous formulations (potentially based on high drug load in solvent/cosolvent formulations) may require a pressurized filtration process and a rotary piston pump to ensure accuracy of fill. This system is ideal for a dedicated process but less flexible in multi-product facilities and typically requires product- specific cleaning to mini-

mize product carry over concerns.

Complexity broadly aligns as a descriptor in which the challenge is presented as drug substance with limited/poor solubility; this also necessitates alternative approaches for development. As a result, the requirement to evaluate alternative presentations, such as suspensions, emulsions, solvent based, or incorporating novel excipients, is also on the rise. About 40% of drugs with market approval and nearly 90% of molecules in the discovery pipeline are poorly water-soluble.[1]

ASEPTIC CHALLENGE

Complex formulation or drug product challenges are classically considered to pertain to the attainment of a target physicochemical characteristic, eg, active concentration/drug loading or particle size distribution. Whilst these remain an initial hurdle to overcome, appropriate solutions must also represent viable options for ultimate scale-up and cGMP manufacture. The complex formulation challenge can often represent the ability to define a robust process that facilitates drug product manufacture to target specification, whilst maintaining a practical aseptic process ensuring sterility assurance.

Like "simple" formulations, complex formulations must be formulated to be safe, stable, and effective in the target patient population. They must align with regulatory expectations and be manufactured under strict aseptic control.

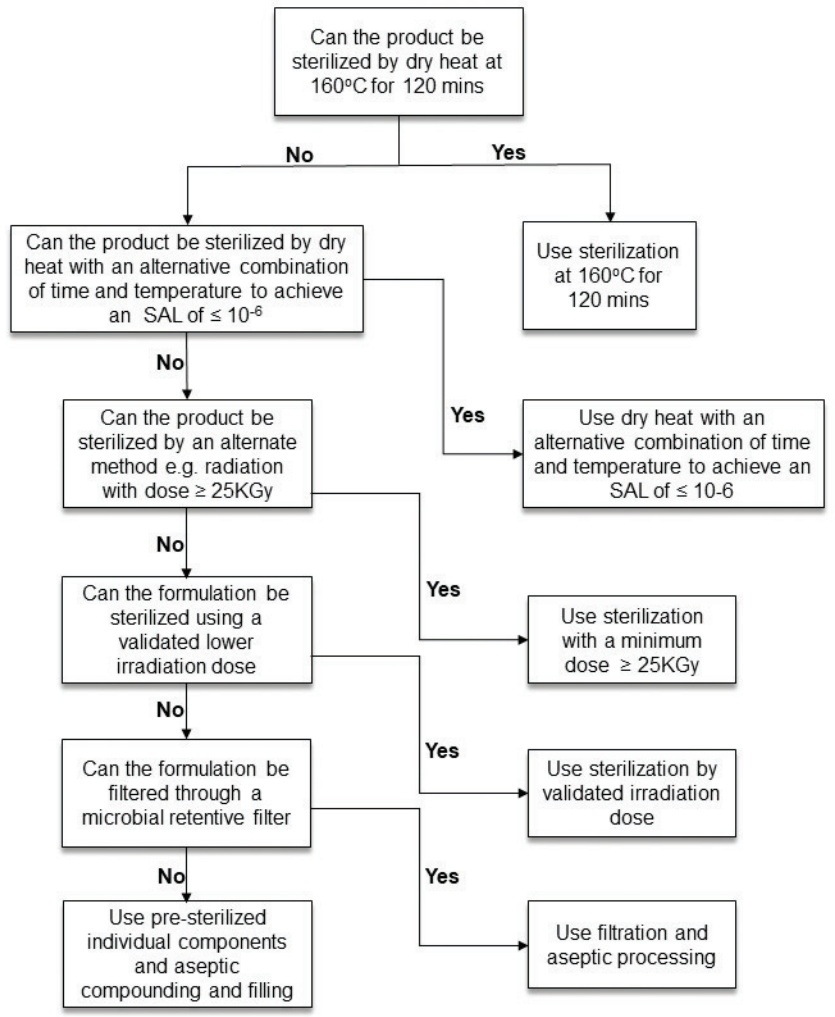
Decision trees for the selection of sterilization methods (CPMP/QWP/054/98) apply to suspension, liposomal, and emulsion formulations and aqueous presentations alike. A decision tree for non-aqueous and suspensions is presented in Figure 1.

Often, by necessity, the controls ensuring sterility of complex parenteral formulations lie close to the base of the decision tree. Design of the aseptic process and most critically, aseptic qualification of the manufacturing team, are of equal importance to the skill of the formulation scientist developing the robust complex formulation. Success is delivered through knowledge transfer and a shared understanding of the broad complexity of the entire process. Teamwork is the foundation for success in delivering complex parenteral products to patients.

ASEPTIC PROCESS DEVELOPMENT

An armory of techniques supporting pre-formulation and formulation development should be utilized at the appropriate phase of product development. Bench-suitable screening tools used at the early, quick assessment stage should be replaced with scalable technologies as lead candidates emerge. A solid appreciation of aseptic controls is required for patient safety and can help guide the transition from candidate selection to process development.

FIGURE 1



EMA Decision Tree for Non-Aqueous Products or Semi-Solid Suspensions

Cheminformatics (pre-formulation), design of experiments (formulation development), and critical process parameter assessment (scale-up) all assist in narrowing the selection process to identify scalable, robust development candidates.

Whilst investigation of formulation strategies can be employed by a skilled formulation scientist/group to explore solubilization, stabilization, and robustness of parenteral drug candidates, the approach requires parallel supporting analytical capabilities to ensure prompt data-driven development strategies.

As an example, a poorly soluble drug substance may be developed as a liposomal product that may be assessed for suitability using high shear, high pressure, or ever-maturing microfluidics processes. The risks/benefits of these various approaches can be rapidly assessed with complementary analytical techniques. Analytical support using HPLC/UPLC techniques with varied detectors, particle size measurement using laser diffraction, and electrophoretic techniques enable the team to both screen and develop candidate formulations.

The connection between formulation scientist and the aseptic manufacturing team is equally important. Assume a suspension product well suited to a high shear, overhead mixing process. At bench scale, a screen of various input particle sizes, excipient and surfactant selection, mixing design, and filling design may well deliver the precise target product specification. If, however, the product cannot be terminally sterilized (via steam or irradiation), reliance on a wholly aseptic compounding and filling process carries significant risk. Here, knowledge of the limitations on scale-up may more readily direct the project team to consider a closed system process with sterile, irradiated API charged via sterile connector or port to vessel, vehicle introduced via aseptic filtration, and an in-line high shear mixer loop delivering particle size control. An automated, barrier system filling utilizing equivalent pump technology as the lab process delivers fill accuracy, content uniformity, and assurance of sterility.

EXTENDED NETWORKS

Technology transfer may be from laboratory collocated with the cleanroom facility or may be to another site, facility, or indeed another vendor. Timely progression through pre-clinical and clinical milestones is as vital as ever for pharmaceutical companies. Design at the bench without an eye on the aseptic GMP process is not an option.

The close communication and sharing of knowledge are vital as a product transfers to the GMP environment and key to success in streamlining development of complex formulations. Single-site formulation and analytical development, combined with GMP manufacture is highly advantageous. This continuum allows retention of product knowledge; it both de-risks the transfer to GMP manufacture and reduces timelines associated with parenteral processes with inherent added complexity.

Support from a network of suppliers (eg, container suppliers, glass specialists, single-use/sterile connection technology vendors, containment solutions providers, and alternate sterilization capabilities) is extremely valuable in supporting the design of complex formulations.

At the heart of all this lies the team; a strong culture of learning, detailed training programs, and a commitment to continuous improvement are key to developing the baseline skills in aseptic processing and growing knowledge and confidence in the evolving trend to more complex aseptic processes and products.◆

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BIOGRAPHY

Dr. Iain MacGilp is the Director of GMP Manufacturing, AMRI Glasgow. He earned his PhD in Chemistry from the University of Strathclyde, Glasgow. He has been with AMRI for 12 years at its Glasgow site. Prior to that, he spent 11 years with GSK in chemical development and broader CMC development roles.

DEVICE DESIGN

Quality-by-Design Approach to Enable High-Dose Drug Delivery With Autoinjectors

By: Patrick Le Gal

ABSTRACT

The challenges associated with designing self-injection systems to deliver biological drugs (ie, biopharmaceuticals) into the subcutaneous space carries very specific challenges relative to those required for the safe and efficacious delivery of traditional pharmaceuticals. For example, biological drug formulations are often more viscous (up to 30 cp and more) and often require larger dosing volumes (up to 2 ml and beyond). These parameters often exceed the capabilities of traditional delivery methods and require new innovations, such as large-volume autoinjectors, that push design constraints to the limits of what is possible while challenging designers to manage competing requirements. In order to accommodate such advances, BD deployed a quality by design approach to manage all the unavoidable competing requirements and to propose a solution that balances performance, robustness, and usability. Two concrete examples of design optimizations and trade-offs are presented, highlighting the value of such patient centric development.

THE CHALLENGE OF BIOLOGICAL DRUG FORMULATION

Biologics, such as monoclonal antibodies (mAbs), pose a number of challenges in formulation development for drug manufacturers. These drugs are usually highly concentrated in order to enable subcutaneous injection. This can lead to high viscosity and can raise concerns of potential drug destabilization, ie, aggregation.

Drug manufacturers are therefore dealing with competing requirements in biologics formulation in order to achieve desired performance. This requires making an acceptable trade-off between the following outcomes:

- Sufficient concentration to achieve the targeted efficacy
- Acceptable range of viscosity that directly affects the force required to deliver the solution

FIGURE 1

BD Physioject™ – 1-mL autoinjector successfully launched 8 years ago

- Manageable volume to enable the subcutaneous delivery with handled injection device
- Required stability during the entire targeted shelf-life
- User-friendly drug delivery solution for optimal patient adherence to chronic treatments

Beyond enabling the administration of such biologics, drug delivery solutions can play an important role in the management of all the aforementioned competing requirements, by providing a "large design space." That could bring some additional degrees of freedom and flexibility in drug formulation and also patient-centric design to drive user friendliness and better adoption.

In order to support pharmaceutical companies in their journey and to advance the world of health, BD is developing a new platform of two autoinjectors, called BD Intevia™. The two formats of BD Intevia™ are designed to meet evolving patient requirements and the demand for higher volume delivery of up 2 ml. Our development strategy encompasses patient centricity, robust-by-design approaches, and leverages key learnings from our interactions with more than 500 pharmaceutical companies on their drugs, delivery systems, patient needs, requirements, and constraints. We also apply the learnings and successes of our first launched 1-mL autoinjector BD Physioject™ Disposable Autoinjector in the design approach for our new platform of autoinjector. The BD Physioject™ autoinjector has been commercialized for more than 8 years with more than 50 million units sold to date.

FIGURE 2

BD Intevia™ disposable autoinjector, the new generation of 2-step push-on-skin autoinjectors in 1-mL (a) and 2,25-mL (b) sizes

THE CHALLENGES OF LARGE-VOLUME AUTOINJECTOR DEVELOPMENT

Similar to the development of a biologic formulation, designing a large-volume autoinjector poses specific challenges with respect to balancing competing requirements that must fall within certain margins. The compromise that must be managed at the formulation level (ie, volume vs. viscosity vs. efficacy…) drives competing requirements for the device that must be overcome.

Developing a large-volume autoinjector poses more challenging design constraints compared to a 1-mL autoinjector. Injecting 2 mL of viscous drug with the same time constraint (10 to 15 secs) without compromising the injection comfort mainly driven by needle gauge requires a high-force injection spring. Such a spring, which could be considered as the "device engine," induces specific integra-

FIGURE 3

Injecting 2 mL of viscous drug in a reasonable time drives competing requirements that must be managed

FIGURE 4

Main Requirements	Critical Design Parameters	Critical Design Constraints
Injecting safety & reliably 2ml of viscous drug within 10s to 15s max	• Spring dimensioning (high spring force) • Needle / Barrel characteristics (minimize pressure drop) • Friction force (reduce resistance) • Needle penetration depth (SQ injection)	• Protect the syringe during activation (damping technology & syringe resistance) • Reduce stresses & deformation to ensure safe storage (material selection & design) • Don't impact activation force • Minimize footprint • Conciliate needle extension tolerance with damping technology
Protecting the sensitive drug during the entire shelf life until the time of injection	• Silicon / Tungsten, glue extractibles • Particles (visible & sub-visible) • Container resistance (assembly, drop test , activation)	• Minimize Gliding resistance • Optimize Material selection (platform approach) • Anticipate required Stabilities
Optimizing useability to increase patient comfort and treatment adherence	• RNS removal force & intuitiveness • 2 steps activation (push on skin) • Low activation force • Progressing & end of dose indicator • Ergonomy (foot print & HF)	• High spring force to integrate • Ensure a robust RNS integration (Barrel diameter vs CAP dimensions vs RNS dimensions)

Key critical design parameters for a large-volume autoinjector and associated constraints and challenges

tion challenges that must be mitigated by design:

- Safe assembly on manufacturing lines
- Safe storage of the loaded spring during the entire shelf-life
- Device footprint and usability impacted by spring design parameters (total length, wire diameter, external diameter…)
- Force to activate the device that must be independent from injection spring force value

Figure 4 summarizes the three main requirements and the associated critical design parameters and constraints.

QUALITY-BY-DESIGN APPROACH FOR BD INTEVIA™ 2,25-ML LARGE- VOLUME AUTOINJECTOR

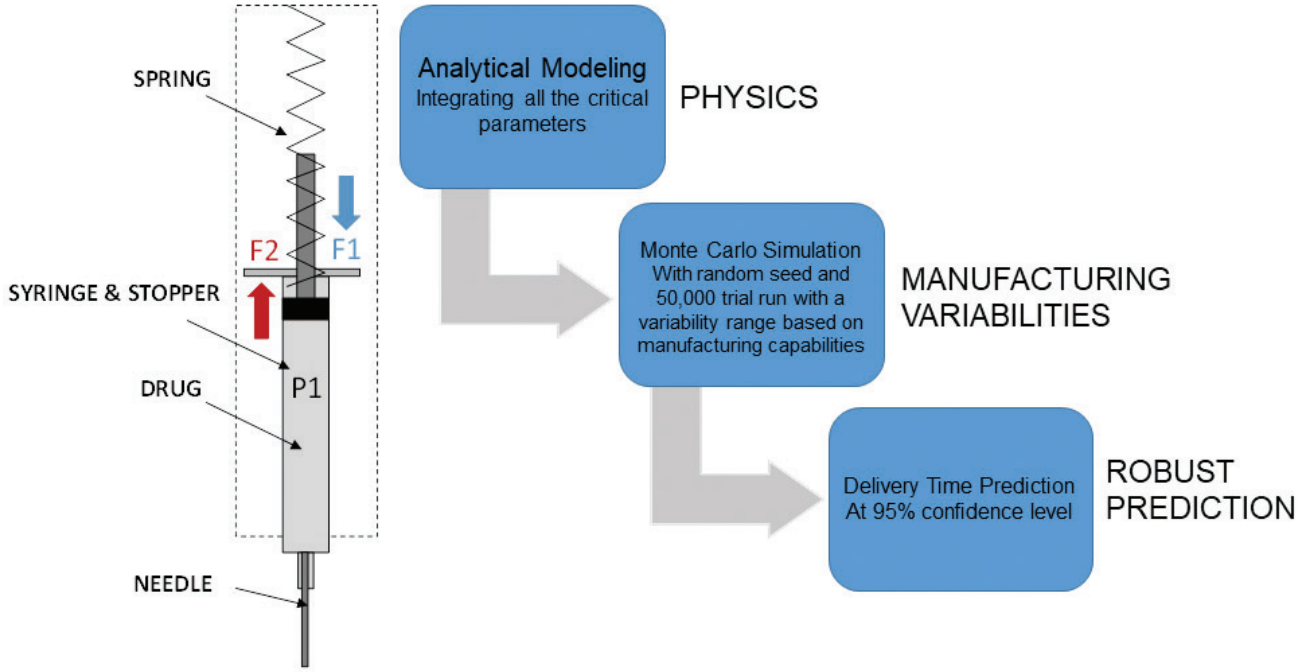
The BD Intevia™ 2,25mL autoinjector has been designed to provide a higher degree of flexibility for pharmaceutical companies, especially for biologics formulation development. Providing a robust drug delivery platform with a higher viscosity limit (up to 30 cP) and a 2mL volume requires a design space, which can accommodate many potential injection configurations. Drug viscosity is a design input, expressed as a value or as a range in the case of platform approaches. Delivery performance, which is essential for patient comfort, is mostly driven by the engine (spring), gliding performance (stopper coating), and needle (main contributor).

Reliable Delivery Time Prediction

Modeling the injection time is key to define reliably the injection conditions integrating all the critical parameters, such as the drug solution (viscosity), the autoinjector (spring force), and the primary container, including as well as its design attributes and mechanical performances (pressure drop, friction…). Such analytical models that integrate equations of physics are commonly used by device manufacturers to drive their design work in order to achieve the targeted performance. Moreover, it is also important to use such a model to assess the dispersion of the delivery time with the integration of the main parameters' variability within their future manufacturing specifications (design for robustness).

Monte-Carlo simulation is therefore systematically conducted by BD to predict reliably with 95% confidence level injec-

FIGURE 5



Critical parameters management and Monte-Carlo simulation to predict drug delivery time integrating all the system parameters variability (device and container) to ensure robustness.

tion time within the upper time limit, leveraging its unique combination of expertise in device development but also in syringe development and manufacturing. An extensive amount of expertise, knowledge, and capabilities around the primary container (ie, analytical, forming, siliconization, needle, rubber, manufacturing capabilities…) in addition to the allocation of dedicated cross-functional and multidisciplinary core team members (device and syringe) allows the optimization of the system architecture, with pragmatic trade-off when required to enable optimized performance and robustness.

Setting a predictable upper delivery time limit is critical to ensure better patient acceptance by avoiding perceptible variabilities that could trigger unexpected behavior (ie, early autoinjector removal due to an overly long delivery time).

Design for Usability

Design for performance and robustness cannot be dissociated from design for usability in the medical device industry, and we need to systematically integrate a "solution-by-design" to ensure Human Factors impacting attributes (injection time, activation force, cap removal force, status indicators…) are well calibrated (targeted nominal value) and controlled (robustness) to secure patients acceptance.

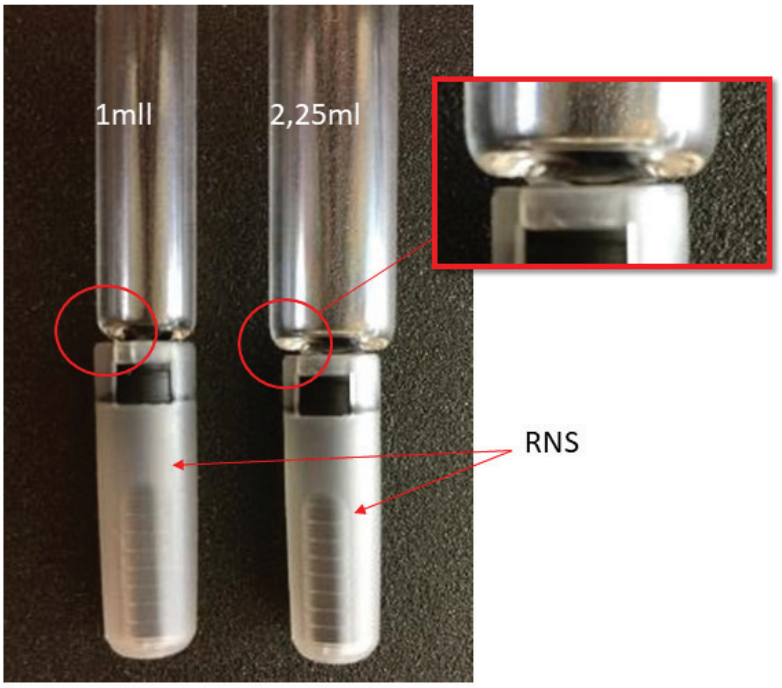
Autoinjector cap removal force is an example of a critical area where we need to pay attention to the integration of the syringe, and more specifically, to the Rigid Needle Shield (RNS).

The 2,25-mL syringe induces specific challenges due to the increased barrel outer diameter (larger than the RNS external diameter) and its induced tip design (smaller tip radius than of a 1-mL syringe, driven by forming constraints). Such design inputs prevent us from leveraging a reliable and proven solution implemented for the 1-mL format (BD Physioject™ and BD Intevia™ 1 mL), creating a challenge to ensure the same level of performance and robustness: complaints level lower than 3 ppm for all failure modes.

We have therefore re-designed and dimensioned the cap removal function for the 2,25-mL autoinjector with the intent to ensure 100% RNS removal with cap pull-off, while minimizing the force required both for the syringe assembly and the force deployed by the patient (Figure 7).

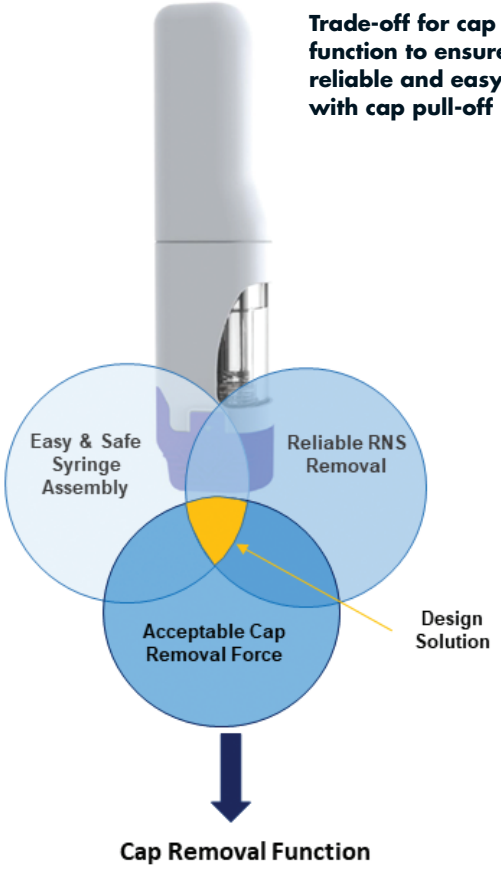
For BD Intevia™ 2,25 autoinjector, all the subsequent steps required to remove the cap and related features that interface with the syringe RNS are strictly

FIGURE 6



Dimensions of the 2,25-ml syringe restrict the design option to grasp reliably the Rigid Needle Shield compared to the 1-mL format

FIGURE 7



decoupled by design. This enables an acceptable cap removal force at any time by avoiding cumulative effect (all the steps are decoupled). The optimization of the function and the associated components therefore included two different objectives: 1) Minimize the maximum force for each sequence and associated variability (performance & robustness) and 2) Decouple all the sequences to avoid any cumulative effect (robustness).

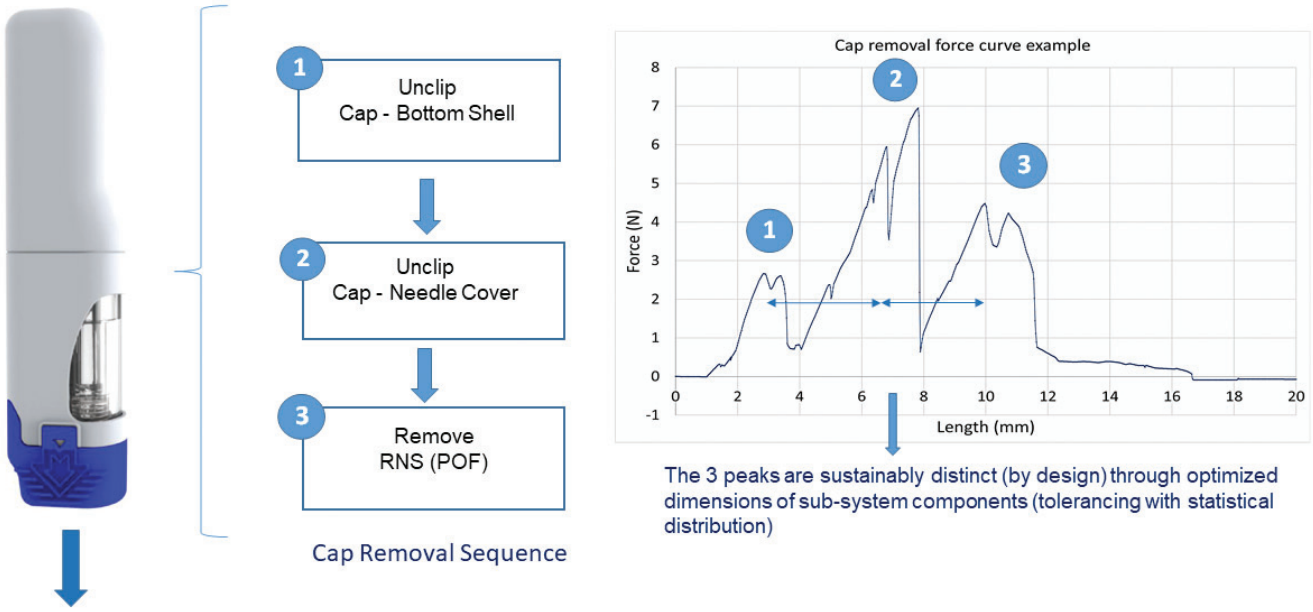
The first objective is ensured by the right dimensioning of the plastic components (clip design) and the selection of the right material (eg, elastomeric needle shield). The second objective is ensured by the right stack-up tolerances (dimensions of all the components with a specific tolerance defined and optimized to ensure the decoupling in worst case).

Such a functional dimensioning approach is similar to the Monte Carlo modelling conducted for delivery time optimization. The use of appropriate statistical distribution (aligned with state-of-the-art manufacturing capability) for all the functional dimensions that are contributing directly to the function allows for full coverage of probabilistic variabilities. The approach ensures proper decoupling of the three forces occurring during the cap removal sequence so that there is no cumulative or additive impact affecting the total acceptable force for the patient as informed by HF studies (Figure 8).

SUMMARY

Because we take into consideration the patient in everything we do, BD deploys a patient-centric approach for developing drug delivery solutions. Design for usability and human factors engineering

FIGURE 8



Cap removal function optimization with "built-in" decoupling ensured by adequate stack-up tolerances.
These data are preliminary data used for illustration purpose. BD Intevia™ 2,25 ml is a product under development and these results are subjected to changes.

cannot be dissociated from design for robustness; otherwise, any sources of variability ("noise factors" in Design-For-Six-Sigma methodology) will trigger a drift in product performance and perception. Patient acceptance is key to ensure better adherence, and device performance must be adjusted and optimized for acceptance, preference, and robustness. Herein, we demonstrated through a case study on the development of the 2,25-mL BD Intevia™ autoinjector how BD deploys advanced methodologies and tools to properly predict and optimize performance, balancing competing requirements and ensuring patient needs are met. Predictable and reliable performance of the drug delivery system over the entire shelf-life is critical to the patient experience and to the brand image and market success of the drug therapy. ◆

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BIOGRAPHY

Patrick Le Gal has been with BD Medical Pharmaceutical since 2006 in different roles in New Product Development and Innovation Management, working with pharmaceutical companies to develop and bring to market drug delivery solutions from prefilled syringes to complex injection systems. He is Mechanical Engineer by training (1993) and started his career in the automotive industry in various R&D positions, where he has focused on system integration, and also on elastomeric systems development and manufacturing. He is currently in charge of the R&D for Advanced Drug Delivery Solutions at BD, such as safety systems, autoinjectors, pens, and wearable injectors, where his responsabilities include innovation, new product development, and sustaining activities in an end-to-end organization.

BIOSIMILAR DEVELOPMENT

Approval of Biosimilar Medicines Through Totality of the Evidence

By: Hillel Cohen, PhD

INTRODUCTION

A biosimilar medicine is designed to match the structure, function, and clinical effect of an already licensed biologic medicine – commonly referred to as a "reference" medicine. The US FDA, EMA, and WHO all apply the same general definition for a biosimilar: a biologic medicine that matches a reference biologic that has been previously approved by regulatory authorities.[1-3] Biosimilar medicines are held to the same safety, purity, and potency standards as all biologic medicines.[1,3-5] To establish biosimilarity, extensive analytical testing confirms structural and functional matching, while confirmatory clinical trials are conducted to show that the biosimilar matches its reference biologic in terms of safety and efficacy.[4-6] As of May 2019, 19 biosimilar medicines have been approved by the FDA, and more than 60 have been approved by the EMA.[7,8]

Biosimilar medicines are developed and tested under the paradigm of the "totality of the evidence" criteria, which verifies the high similarity of biosimilar and reference medicines through head-to-head comparisons of multiple structural and functional parameters, as well as human pharmacokinetic (PK) and pharmacodynamics (PD) studies. This is then confirmed by limited but very directed clinical confirmation of efficacy and safety.[5,6] This article outlines the evolution of biosimilar approvals and describes the process of analytical and clinical testing followed in the development of a biosimilar, with use of data from the scientific literature.

Biologics have been the fastest-growing class of pharmaceuticals in the US, offering treatments for many conditions that long eluded medicinal treatment.[9] Many of the revenue-leading biologics (eg, Humira®/AbbVie, Remicade®/Janssen) are coming off patent. This is potentially paving the way for use of biosimilar medicines in several therapeutic classes, such as oncology, immunology, and endocrinology.[10,11] With continued expansion of the market, experts forecast that biosimilar medicines could save $54 billion in spending on biologics over 10 years.[12]

Sandoz developed the first approved biosimilar in the world: human growth hormone, Omnitrope® (somatropin), approved in Europe in 2006.[1,7] To gain approval, Sandoz presented data from analytical, preclinical, and clinical studies to the EMA confirming that the somatropin biosimilar matched the reference biologic (Genotropin®/Pfizer).[10] Omnitrope was approved by the FDA in 2006 as a new drug that relied in part on reference product data (called the 505(b)(2) pathway) rather than as a biosimilar, because the legal basis for approving biosimilar medicines in the US did not exist at that time.[10]

DEVELOPING THE PATHWAY FOR BIOSIMILAR APPROVAL

Biosimilar medicines are designed to match the structure, function, and clinical performance of their reference biologic. Biosimilar development is possible because technology has advanced to the point that a new biological medicine can be designed very precisely. Moreover, analytical methods are much more sensitive and specific than a few decades ago, which led to a revolution in our ability to analyze protein structures.[5]

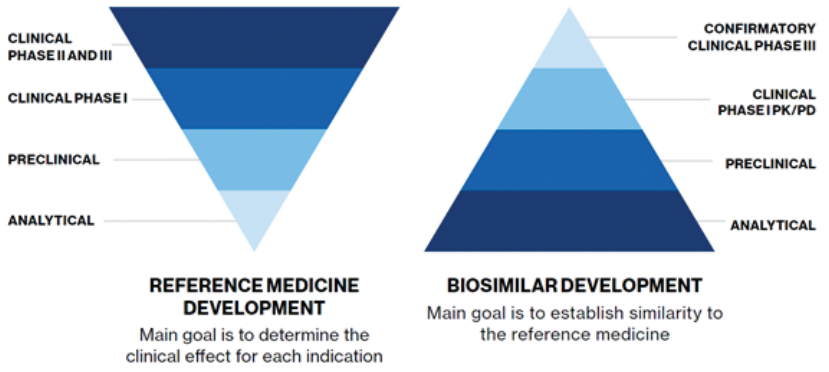
Unlike approval of new medicines, where the aim of the development program is to establish the safety and efficacy of a new molecular entity for treatment of a specific condition in a spe-

cific patient population, the goal of biosimilar development is to demonstrate, by means of head-to-head comparisons, that the biosimilar medicine matches the reference biologic very closely and that any differences that might exist have no impact on safety or efficacy.[5] Experts realized that instead of mandating a single approach for all biological medicines regardless of structure or indication, it would be more appropriate to take a case-by-case approach for individual products including the implementation of study designs with optimally sensitive patient populations and endpoints.[6,9,13]

Multiple different types of comparative data are collected, including analytical tests, biological assays, human PK and PD studies (to assess what happens to the medicine in the body, or what happens to the body when exposed to the medicine, respectively), immunogenicity studies, and if necessary, limited human safety and efficacy studies. It is not necessary to repeat large human efficacy and safety studies because the safety and efficacy of a biosimilar is based on data established in studies of the reference biologic.[5,6] This more specific and streamlined process became the "totality of the evidence" standard.[4,5]

The licensure process for biosimilar medicines in the US was established in 2010, when the Biologics Price Competition and Innovation Act (BPCIA) was enacted.[14] The BPCIA was intended to enable approval of biosimilar medicines to increase treatment options, potentially save lives and decrease healthcare costs through market competition.[3,14] The biosimilar pathway also intended to curtail unnecessary and potentially unethical testing in animals and humans.[9,13] The quantity of data provided with a biosimilar application is very large, although more emphasis is placed on the analytical and biological function data than on clinical data (the opposite is true for reference biologic applications). The rigor of the FDA review is just as high for a biosimilar as was applied to the reference medicine when it was initially approved. Figure 1 illustrates how the biosimilar program differs from that for originator medicinal biologics.

FIGURE 1



Contrast between the standard (351(a)) regulatory pathway to establish safety and efficacy of a new biologic product (left) and the biosimilar (351(k)) regulatory pathway to establish a match between the biosimilar and the reference product (right).[15]

In 2015, Zarxio® (filgrastim-sndz/Sandoz) became the first approved biosimilar in the US, based on evidence from analytical, human PK, human PD, and confirmatory human safety and efficacy studies demonstrating biosimilarity to the reference biologic, Neupogen® (filgrastim/Amgen).[5,8] Zarxio approval was followed by more than a dozen other biosimilars in the US, including, Erelzi™ (etanercept-szzs/Sandoz) and Hyrimoz™ (adalimumab-adaz/Sandoz).[8] Biosimilarity for Zarxio was based on 22 analytical methods evaluating 19 different attributes; more complex biosimilar medicines (eg, Erelzi) have required more than 50 analytical methods for more than 80 attributes.[5]

APPROVAL OF A BIOSIMILAR: "TOTALITY OF THE EVIDENCE"

Approval of a biosimilar is based on the "totality of the evidence" standard, which can be defined as the sum of data from analytical, preclinical, and clinical studies.[5,6] According to the FDA:

"There is no one size fits all approach to biosimilar product development. The goal of a biosimilar development program is to use a "totality of the evidence" approach to demonstrate biosimilarity to the reference product, not to independently establish safety and effectiveness of the proposed biosimilar."[3]

The FDA evaluates biosimilar medicines on a case-by-case basis, mandating or waiving certain types of studies based on the nature of the molecule and its intended use.[3,5,6] The goal is to prove high similarity to the reference biologic, not to directly test the safety and efficacy of the biosimilar medicine.[3,5,6]

The totality of the evidence standard is accepted worldwide, including by the FDA, EMA, and WHO.[4,5] Totality of the ev-

"Unlike new medicines that are approved on the basis of extensive clinical data, often in multiple indications and in different patient populations, biosimilar medicines are developed using the concept of totality of the evidence. This means biosimilar medicines and their reference biologics are compared analytically, functionally, and then in a more limited human clinical program to verify the high similarity of the two medicines."

idence signifies verification that patients can expect the same clinical performance when using the biosimilar as when using the reference biologic, and that there will be no clinically meaningful differences with respect to safety or effectiveness.[5] In short, according to the FDA:

"…the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components … there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."[6]

DEVELOPING A BIOSIMILAR

Biologics, both reference and biosimilar medicines, are manufactured from living organisms. As such, it is normal to have lot-to-lot variability for all biological medicines. No lot of a biological medicine is an exact replica of prior lots, but all are within ranges that are known to be safe and efficacious.[4,5] These ranges are the development target for the corresponding biosimilars. Likewise, a biosimilar is not a precise replica of its reference biologic, but the differences are acceptable if they are not clinically meaningful.[1,3-6]

Analytical Comparisons

The goal of the analytical evaluation is to ensure that the biosimilar is within variability of the reference biologic across the multiple assays used, and that any minor difference is not clinically relevant.

Analytical studies are intended to demonstrate a molecular (physicochemical) and functional (bioassay) match to a previously-approved reference biologic.[4,5,16] Structural and functional attributes include primary structure (ie, identical primary amino acid sequence), higher-order structure (the three-dimensional shape), biological activity (as measured by bioassays that can include receptor binding or cell-based assays), protein content, sub-visible particles, impurities, thermal stability, post-translational modifications including glycosylation and higher molecular-weight variants or aggregates.[4,5,10]

Any residual uncertainty from the analytical similarity assessment is examined for potential clinical relevance by means of human PK and PD studies, and if appropriate, in safety and efficacy studies.[5,16] Analytical and functional data establishing molecular similarity are the foundation for the totality of the evidence model for biosimilar medicines.[5]

State-of-the-art analytical methods are used to characterize both the biosimilar and the reference biologic.[5,10] Many analytical techniques in use today did not exist at the time of approval of the reference biologics. Additionally, these new analytical methods may bring to light batch-to-batch variability in reference biologics that was previously unrecognized.[5] These analytical methods are more sensitive than clinical studies and enable biosimilar developers to detect sub-clinical differences, giving them increased importance in evaluating biosimilarity.[6]

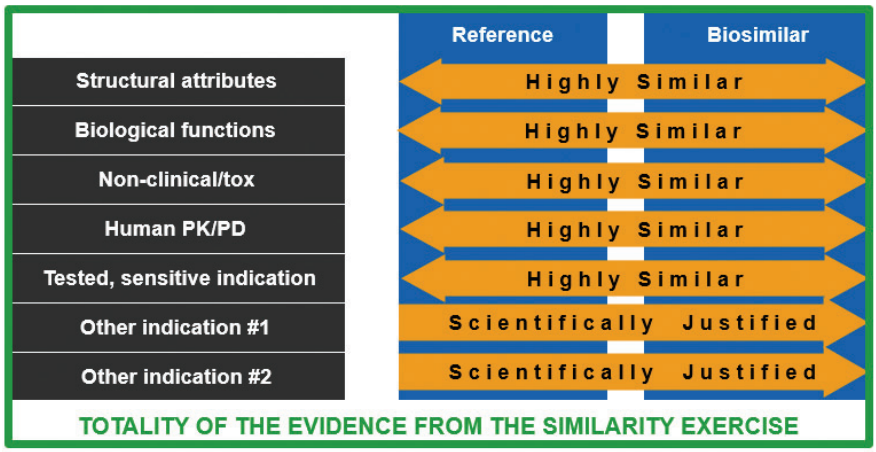
Preclinical & Clinical Studies

Biosimilar medicines are tested in a stepwise fashion, with a targeted preclinical and/or clinical program following structural and functional characterization. The extent of the preclinical and/or clinical program depends on the residual uncertainty that may exist after the analytical and functional comparisons of the biosimilar and reference biologic.[3-5,10,16] The targeted clinical development program is scientifically justified because the reference biologic has already been demonstrated to be safe and effective in the approved indications.[2,4,5] The goal is not to prove it again with a biosimilar, but to confirm the absence of any clinically meaningful differences versus the reference biologic.[4-6,10]

In the clinical stage of biosimilar development, human PK, and, if applicable, PD studies are central. They are sensitive tools to ascertaining whether there are potential clinically relevant differences between a biosimilar and its reference biologic.[5,13,16] Human PK studies are typically conducted in a healthy subject population because they are not receiving any other medications or have comorbid conditions that could confound the results.[4,5] Immunogenicity studies are also conducted in a sensitive population and must be long enough in duration to allow development of antibodies after extended exposure to the biologic medicinal product. In addition, the studies must assess for the development of neutralizing antibodies that could have clinical implications.[5]

Confirmatory safety and efficacy studies may be conducted in a patient population, although again, these are designed to detect any clinically relevant differences that may exist, and not to reestablish safety or efficacy of the active substance.[4,5] As a result, the studies use a sensitive sub-population and endpoint which may be different from those used to establish *de novo* the efficacy and safety of an active substance.[6]

FIGURE 2



The concept of extrapolation in the context of biosimilarity. Once high similarity is demonstrated at multiple levels between a biosimilar and reference biologic, including clinical confirmation in a sensitive patient population, then it is justified to assume that the biosimilar will also have a similar safety and efficacy profile to the reference biologic in less sensitive indications that share the same mechanism of action.[17-19]

Extrapolation

In line with the aforementioned, it is not necessary to repeat studies in all indications for which the reference biologic is approved because the concept of extrapolation can be applied. Extrapolation allows approval of a biosimilar for other indications for which the reference biologic is approved, even if the biosimilar was not studied specifically on those indications.[3,6,10] Extrapolation is not a mere assumption of efficacy and safety for a different indication; it must be rigorously supported by scientific evidence.[3,6,10] The essence of extrapolation is that if high similarity is demonstrated in structural attributes, biological functions, human PK, human PD, and clinical efficacy and safety in a sensitive patient population (including immunogenicity), then it is justified to assume that the biosimilar will also have a similar safety and efficacy profile to the reference biologic in less sensitive indications that share the same mechanism of action.

The concept of extrapolation has been used by health authorities for decades. For example, when a major manufacturing change is introduced for an originator biologic that may result in changes in product characteristics. If the results confirm that the clinical performance has not changed, health authorities extrapolate and approve that biologic made with the process change for use with all indications, including those indications and populations that were not studied with post-change material. Clinical trials comparing the biosimilar to the reference biologic for each indication are not only unnecessary, but would also obviate the goals of expedited biosimilar approval (ie, the BPCIA).[5,6] Further, extrapolation in the biosimilars class has become widely accepted by health authorities – continuing to play a substantial role in biosimilar approvals.[6,17]

Substitution & Interchangeability

Prescribers have the ability to prescribe the medication they believe is most

appropriate for their patients. As such, they have the ability to switch from a reference biologic to a biosimilar at any point in time they deem appropriate. However, for a pharmacist to substitute a biosimilar for a reference biologic without first obtaining permission from the prescriber, the biosimilar must be designated by the FDA as "interchangeable."

Interchangeable biologics are evaluated to the same level of quality standards as described previously.[3,9] The FDA, however, has indicated that for products to be designated as interchangeable, additional, and different data will be required. In particular, for products administered to a patient more than once, manufacturers will need to conduct an additional clinical study in which patients are switched back and forth at least three times between the reference biologic and biosimilar. The concept of interchangeability is unique to the US – no other country has a separate interchangeability category. Many authorities believe that whether an approved biosimilar is designated interchangeable or not, the risk posed by switching between the biosimilar and the reference biologic is no greater than the risk posed by using the reference medicine only. To date, no company has sought an interchangeable product designation in the US for a biosimilar.[20]

Public Acceptance of Biosimilar Medicines

The mission of the FDA is to be "responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices."[21] Biosimilar development is strictly regulated by the FDA and each application undergoes very thorough review by the Agency based on different but similarly stringent requirements compared to their reference biologic. This ensures their quality, safety, and efficacy so patients and prescribers can expect the same benefits as the reference biologic. While the development and regulatory review of a reference biologic primarily focuses on the Phase III clinical data, the biosimilar development and review focus on comparisons to the reference biologic that are most sensitive to detect differences.[3,5]

Providers and patients must be educated about the biosimilar approval process to help them understand and then accept these products.[1,3,5] This may be a challenge for prescribers as they are trained to understand and accept medicines based on extensive clinical data, such as directly observed improvement in a disease state. For establishing biosimilarity, the most important data are analytical test results comparing the structure and function of a biosimilar and reference biologic. Patient education is also important as biosimilar medicines are utilized to reduce costs and increase access. It must be carefully explained to patients that there will be no difference in efficacy or safety if they receive a biosimilar in place of a reference biologic.[1,3,5,6]

SUMMARY

Unlike new medicines that are approved on the basis of extensive clinical data, often in multiple indications and in different patient populations, biosimilar medicines are developed using the concept of totality of the evidence. This means biosimilar medicines and their reference biologics are compared analytically, functionally, and then in a more limited human clinical program to verify the high similarity of the two medicines.

Because this is a relatively new concept for providers and their patients, education is necessary to increase understanding of what these products are, how they are approved, and the fact that patients can expect matching safety and efficacy of a FDA approved biosimilar and the respective reference biologic. Knowledge and acceptance of biosimilar medicines are critical to helping fulfill the promise of the BPCIA for improving access to high-quality medicines while decreasing societal healthcare costs. ◆

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BIOGRAPHY

Dr. Hillel P. Cohen is Executive Director of Scientific Affairs at Sandoz, helping explain the principles of biosimilars and biosimilar policies to the healthcare community, patient advocacy groups, and health authorities. Dr. Cohen led Sandoz efforts for the first biosimilar presentation (Zarxio®) to an FDA advisory committee and participated in BsUFA 2 negotiations on behalf of industry. He helped co-found the Biosimilars Forum, where he is currently co-chair of the education committee. He is also a member of the education and regulatory committees of the Biosimilars Council, a division of the Association for Affordable Medicines. Dr. Cohen earned his BA from New York University and his PhD in Biology from Dartmouth.

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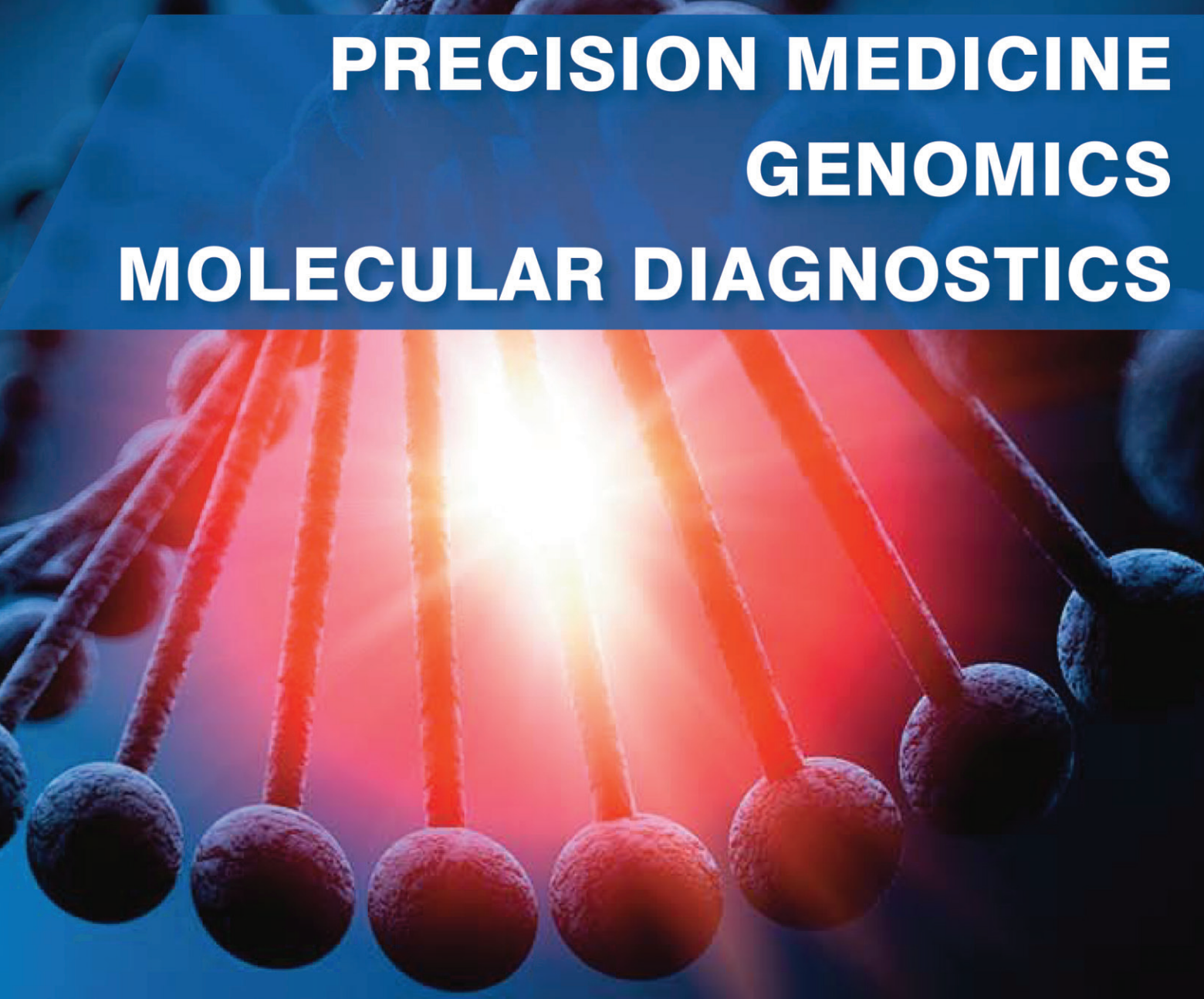


The Frost & Sullivan Global Life Sciences Program helps you identify stakeholder dynamics as the healthcare system transitions from acute care into integrated care.

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

Special Feature

Outsourcing Formulation Development & Manufacturing: CDMOs Shift to Offer More Specialized Services

By: Cindy H. Dubin, Contributor

As drug products become more complex, there is increasing customer demand for relationships with contract development and manufacturing organizations (CDMOs) that have core competencies in highly specialized formulation and process technology areas.

One of these specialty areas is complex molecules. Biotech companies developing novel biologics are increasing in the market, thus there is an increase in outsourcing development services to BioCDMOs. To serve the needs of this market, companies like FujiFilm Diosynth Biotechnologies are expanding their bio capabilities to offer advanced manufacturing technologies. FujiFilm predicts the BioCDMO market to grow at more than 8% per year.[1]

Another area of expertise where pharma is relying on CDMOs is in cell and gene therapy. Industry insiders expect gene therapy manufacturing market to boom and grow at rates ranging from 15 to 20%.[2] Benefits of partnering with a cell or gene therapy CDMO include scalability, speed to market, access to technical expertise without overhead costs, and cost efficiencies. Demand for specialized manufacturing and clinical trial support for cell and gene therapies has resulted in more than 40 companies offering these services.[3] And the market continues to expand. As of press time, Catalent acquired gene therapy CDMO Paragon Bioservices for $1.2 billion. Catalent believes that the addition of this capability from the Maryland firm will help tap into the strong gene therapy market.

No matter the area of specialty, CDMOs find they must shift toward providing value-added services by establishing themselves as a one-stop-shop for pharma clients "When you work with multiple contract services organizations during the drug development and manufacturing process, it takes more time, increases costs, and involves greater risk," says Robert Lee, PhD, President, Particle Sciences. "If there are five or six

Often-complex molecules require specialist handling to ensure protection of both operators and the environment (PCI).

organizations working on different elements of the same project, it's more difficult to manage and you need to ensure that someone is keeping track of all the players and arranging the logistics. For example, we've found that when another company does the analytical work for a client, we can wait weeks for the analytical data we need to help support our formulation efforts. When we do the analytical work ourselves, then those delays don't happen and we are in control of the information flow."

Working with a one-stop-shop means that everything is done in one place, removing time and risk mitigation concerns. This is a particularly critical issue when transferring between late-phase clinical to commercial. Dr. Lee says some CDMOs can get a pharma to Phase 1/2, but transferring a complex formulation to another CDMO can involve cost and time.

In this exclusive *Drug Development & Delivery* magazine annual report, several CDMOs discuss their formulation development and manufacturing capabilities for bio/pharma companies of all sizes.

Ascendia Pharma: In-House Nanotechnologies Screen Formulations

Project sponsors are looking for a CDMO that is flexible with a proven record of quality, and has the ability to complete the project quickly to the proof of concept stage. This can prove challenging for more complex compounds. An increase in API complexity, breadth and depth of formulation expertise in resolving compound physical-chemical and biopharmaceutical problems, and the ability to strengthen the intellectual property position of the client's products are becoming a lead criterion when selecting a CDMO.

Jim Huang, PhD, CEO of Ascendia Pharma, says Ascendia's one-stop-shop CDMO is adept at tackling a compound's formulation challenges within a very tight time window. In one case, he says Ascendia was awarded a lipid project transferred from a previous CDMO. "Within 3-4 months, we did more than resolve the stability issue that would otherwise need a toxicity qualification for a new impurity," he explains. "We enabled room temperature storage instead of 'store under refrigeration,' as well as resolved the formulation capsule's incompatibility that was causing an extremely low yield. In another case for a SEDDS lipid formulation, we were able to improve the drug loading and increase the API bioavailability two- to three-fold from the original formula. The result was a dramatic reduction of dose burden from 25 capsules/day to less than 6 capsules/day."

In addition to traditional formulation expertise in oral, controlled release, parenteral, and topical dosage forms, Ascendia often conducts formulation screening, development, and GMP manufacturing using its three in-house proprietary nanotechnologies: Nanosol, AmorSolk, and EmulSol. "In most cases, the outcome of formulation in PK studies is outstanding, which enables a dramatic increase in bioavailability and a dose-expose linearity for GLP toxicity and first-in-man studies for new compounds or repurposing 505 (b)(2) products," says Dr. Huang.

Cambrex: Responding to Formulation Trends & Regulatory Changes

As a full service CDMO, Cambrex is witness to many industry trends. First, as the market evolves, new products are being developed in smaller batch sizes than in the past, due in part to the increasing number of drugs being developed for selectively niche patient populations, explains Maryse Laliberté, Vice President & General Manager, Cambrex. "This is a change from the previous paradigm where historically drugs were developed with multiple indications in mind. We are currently seeing many new drugs in the pipeline being developed with a focus on very specific and orphan diseases."

She adds that more targeted, smaller patient populations have driven demand for a niche type of support, which can mean a more complex manufacturing process.

"As companies work on drugs for smaller patient populations, the reduced quantities of drug material required during the clinical trial process potentially means a more simplified supply chain and the sponsor company no longer has to manage multiple CDMOs as in the past," adds James E. Cherry, Vice President, General Manager, Cambrex. "Additionally, developing for smaller populations reduces clinical trial costs and can help expedite the approval process for the product."

When it comes to regulatory approval, Mr. Cherry says it is critical to understand that companies are looking for full support. This has caused a growing use of third-party consultants, as well as heavy reliance on the expertise of CDMOs. He says: "Particularly true is that smaller or virtual companies bringing new molecules to market are looking to work with a CDMO

much earlier in the process — sometimes starting at clinical phases — and more often are keeping the product in house for longer, rather than the historic notion of licensing or divesting to Big Pharma after Phase 2. Drug complexity aside, two-thirds of new drug approvals in the clinical pipeline is coming from small and emerging pharma companies who are leaner than the traditional pharma companies in terms of support functions such as regulatory affairs."

New regulations are coming into play with respect to pediatric dosage and formulation development. This is of particular importance to drug manufacturers seeking to create alternative formulations for younger patients. "The industry, and in particular Big Pharma, is placing a stronger focus on developing pediatric formulas as they look to extend their current patent on their existing adult formulas," says Mr. Cherry.

Metrics Contract Services: Answering a Range of Formulation Development Requests

As a full-service CDMO, Metrics Contract Services has received requests for a range of formulations. Joe Cascone, Vice President, Metrics Contract Services, says dry granulation (roller compaction) has become the go-to granulation technique for solid-oral dosage, as it lowers the overall processing cost and helps avert potential stability-related challenges caused by moisture in the wet granulation technique. "State-of-the-art compactors, such as the Gerteis, have allowed development of robust roller compaction formulation for capsules as well as tablets."

And, for powder-in-capsule formulations, a popular alternative to clinical formulations, he says clients are moving towards plant-based HPMC capsule shells instead of traditional gelatin capsules to accommodate patients who are mindful about from where excipients are derived and prefer plant-based options.

"Overall, sponsors have asked us to develop a variety of formulations, ranging from simple immediate-release dosage forms requiring direct-blend encapsulation to complex mixed-dosage forms with both immediate- and sustained-release attributes so patients can avoid taking multiple daily doses and improve their compliance," says Mr. Cascone. "The choice of formulation depends on various factors, including biopharmaceutical, physicochemical properties, stability, and the pharmacokinetic properties of the API."

Evonik: Competencies in Polymeric & Lipid Nanoparticle-Based Formulations

As a CDMO partner for advanced drug delivery, Evonik supports customers worldwide in the development and cGMP production of complex oral and parenteral drug products. Danielle Clay, Global Strategic Marketing and Business Development Director for Drug Delivery at Evonik, says that for oral drug products, demand continues to strengthen for functional excipients that enhance drug efficacy, improve patient compliance, and address poor solubility and low permeability. Recent program examples at Evonik include a desire for improved swallowability, the use of combination polymers, and the application of additive manufacturing technologies for the 3D printing of personalized oral solid dosage forms.

"For the development of oral drug products, we support customers across multiple functionality areas including immediate-, delayed-, and sustained-release, as well as specific custom areas such as colon targeting and pulsatile release," she says. Areas of formulation focus include the development and production of orphan drugs for accelerated entry into clinical Phase 1or 2 trials, oncological drugs for early-stage human clinical trials, and pediatric formulations such as multiparticulates and mini-tablets.

In the complex parenteral drug product space, Ms. Clay sees strong demand for formulations with high potency APIs, gene-based therapies such as mRNA, and extended-release microparticle or nanoparticle technologies. Formulation development requests for complex injectables cover a range of target product profiles but tend to focus more on precision delivery, improved efficacy, and better patient compliance. Formulation project examples include local delivery to the eye, knee, joint or tumor; achieving a specific rate and duration of API release; better penetrating target cells for improved API uptake; and reducing systemic toxicity. "We also see more companies undertaking early formulation feasibility studies, while demand for process development, scale up, and cGMP manufacturing continues to increase, especially for aseptic processing," she says.

For polymeric-based parenteral formulations, Evonik supports excipient selection and initial formulation feasibility testing through to commercial production and filling. "With many complex parenteral products requiring aseptic manufacturing, we are also experiencing strong demand for aseptic powder filling at both clinical and commercial scale," says Ms. Clay.

Given the increasing complexity of oral and parenteral drug products, Ms. Clay says it is impossible for any CDMO

Evonik Birmingham Laboratories facility in Alabama supports the growing demand for parenteral excipients and drug delivery services.

to offer best-in-class services across every drug delivery technology. But, she says Evonik has established core competencies in the development and production of polymeric and lipid nanoparticle-based formulations.

HERMES PHARMA: Novel Formulations Easily Deliver Therapeutics

People are increasingly seeking ways to proactively improve their health and prevent problems, which has led to a growing market demand for personalized medicinal products and food supplements. As a whole, the increasing popularity of supplements has broadened the market for user-friendly dosage forms such as effervescent tablets, orally disintegrating granules and, most recently, hard pod capsules like HERMES NutriCaps.

"The latter are compatible with hard pod coffee machines and are used to prepare hot drinks containing the supplement or medicine," explains Dr. Detlev Haack, Head of R&D at HERMRES PHARMA.

Despite the novelty of the approach, Dr. Haack says this dosage form is gaining traction, with cough and cold remedies being the first treatments to be released in these pods. "The hard pods provide people with a quick, convenient, and safe way of taking food supplements. They not only meet the need for high-quality and tasty supplements, but their ease of use can help people comply with their health goals and feel empowered to achieve them."

A further key advantage of hard pod capsules is that they can meet the demand for traceability in healthcare products, as the ingredients can be traced directly back to the farmer or to the company holding the nutrient.

"Most sponsors that approach us are looking to develop user-friendly dosage forms, as they recognize the continually growing demand and want to work with experts to develop a product line in this expanding market," says Dr. Haack.

In a survey of 2,000 people in the US and Germany[4], more than 50% of the participants reported difficulties swallowing traditional tablets and capsules, and about 40% said that they would prefer products that have a pleasant taste and are easy to integrate into their daily routines. As such, Dr. Haack says there is demand for products that are both easy to swallow and convenient to use. For example, orally disintegrating granules are popular for taking 'on the go' and instant drinks in sachets. However, he says, HERMES is increasingly being asked for novel forms like hard pods. "We're frequently told by our customers that the demand for user-friendly products is continuing to grow, and we are committed to making the necessary investments to ensure we can meet the market need."

When developing a novel form like the hard pod, Dr. Haack says risk analysis was conducted. "We anticipated that the authorities would ask whether coffee machines were safe 'medical devices' for preparing medicinal drinks. In our risk analysis, we found strong evidence that using a coffee machine is much safer than preparing hot water in a kettle. We also found that using the hard pods with a coffee machine enables consistent, correct doses, with the freshly prepared drink remaining stable for at least an hour after preparation."

Currently, HERMES is developing a new user-friendly dosage form of an existing treatment for cystitis. The treatment consists of D-Mannose, a naturally occurring sugar that prevents bacteria from attaching to the bladder lining. "We originally identified the product in a powder dose form in Eastern Europe, where it is manufactured as a widely-used dietary supplement to support urinary tract health," Dr. Haack explains. "In clinical tests, we discovered that D-Mannose is just as effective against cystitis as antibiotics and, even more interestingly, it doesn't produce any side effects. Its original powder form did not optimize compliance, as it needed to be dissolved in water three times daily. This revealed a clear need for a more user-friendly and convenient dosage form, which we are currently developing as a HERMES NutriCap hard pod. This highlights how CDMOs can develop new, optimized dosage forms for existing effective therapeutics, providing low-risk opportunities to enter a growing and potentially profitable market."

Particle Sciences: Tackling Challenges of Poorly Water-Soluble Molecules

A number of factors in the market are reshaping the approach to dosage forms, resulting in a rise in non-traditional dosage forms such as nasal sprays and drug-eluting implants. One reason for taking these new approaches is the number of drugs that contain poorly water-soluble APIs.

"When poorly water-soluble drugs are delivered through traditional dosage forms such as oral solid dose, they fail to dissolve, have severely limited bioavailability, and therefore have limited therapeutic effect," says Robert Lee, PhD, President, Particle Sciences. "There are multiple techniques available to increase the solubility or dissolution rate of drugs and improve their delivery, particularly the use of amorphous solid dispersions and nanoparticle formulations."

Alongside the issue of poor solubility is the increase in 505(b)(2) approvals – an FDA regulatory pathway that involves taking existing, marketed APIs into a different route of administration. These approvals grew 50% last year and this regulatory path has become increasingly popular over the last decade, usually involving innovative dosage forms or drug delivery methods that are considered complex, explains Dr. Lee.

"Navigating the regulatory pathway and ensuring a molecule reaches the clinical trial phase is relatively straightforward for simple dosage forms such as an oral solid dose or a sterile injectable solution, but with more complex formulations involving nanoparticles, there are a lot of layers," he says. "It's hard enough to develop a complex formulation that tackles poor solubility without the added obstacle of inadequate regulatory knowledge that could see a product fall at the first hurdle."

Preventing failures related to complex formulation challenges is something Dr. Lee takes seriously. "Clients sometimes come to us with formulations that have been developed on benchtop only or by organizations that just don't have experience in complex dosage forms," he explains. "We take on these sub-optimal formulations and use a more scalable process in conjunction with optimizing the formulation to make a much better product that is acceptable for GMP production and commercial production."

HERMES NutriCaps are hard pod capsules that deliver medicine and supplements via a common coffee machine.

When the API is a particularly challenging molecule, it is important to come up with better formulation methods. For example, one molecule Particle Sciences worked on recently was poorly water soluble. Dr. Lee says a novel formulation was identified that was comprised of GRAS liquids that had strong solubilization characteristics, and Particle Sciences filed a provisional application. "This approach enabled us to produce a solution with the required pharmacokinetic profile to match the commercial product given by a different route of administration," he says. "By doing so, we were able to provide our client with additional intellectual property protection for their asset."

PCI Pharma Services: Troubleshooting Challenges of Potent Products

Over the last year, PCI has seen a continued increase in the number of highly potent molecules at early-stage development. These often-complex molecules require specialist handling to ensure protection of both operators and the environment. Additionally, APIs can be in short supply, expensive, and time-critical in terms of the development program.

"Clients are seeking suppliers who are experienced in the handling of such molecules able to offer multiple options in terms of the development pathway," says Kat Jones, Director of Marketing and Commercial Operations, International, PCI Pharma Services.

PCI has seen an increase in requests for early-stage drug-in-capsule (DIC) technologies whereby the API is filled directly into capsules either as neat API or a simple blend formulation. This approach, says Ms. Jones, enables the client to either accelerate the development program further or to 'fail and fail fast,' therefore delivering both time and cost efficiencies.

"We are being asked to tackle almost all formulations as expected for any CDMO, with a high percentage being solid oral dosage forms," she says. "In the last 12-18 months, however, we have experienced a significant increase in development and manufacturing programs where the final dosage required is a non-sterile oral liquid, a high proportion of which are also classified as highly potent. As with the manufacturing of a solid oral dosage form, any drug product in liquid form containing a highly potent API is subject to specialist handling requirements with additional controls."

And, as with any CDMO, challenges arise. A recent example involved a formulation whereby the active was classified as potent. The product contained a very low dosage within the tablet core of a sustained-release formulation, explains Ms. Jones. "When the previous CDMO was unable to meet the assay and content uniformity requirements, PCI was approached to transfer the product, troubleshoot the challenges, and ultimately deliver the product."

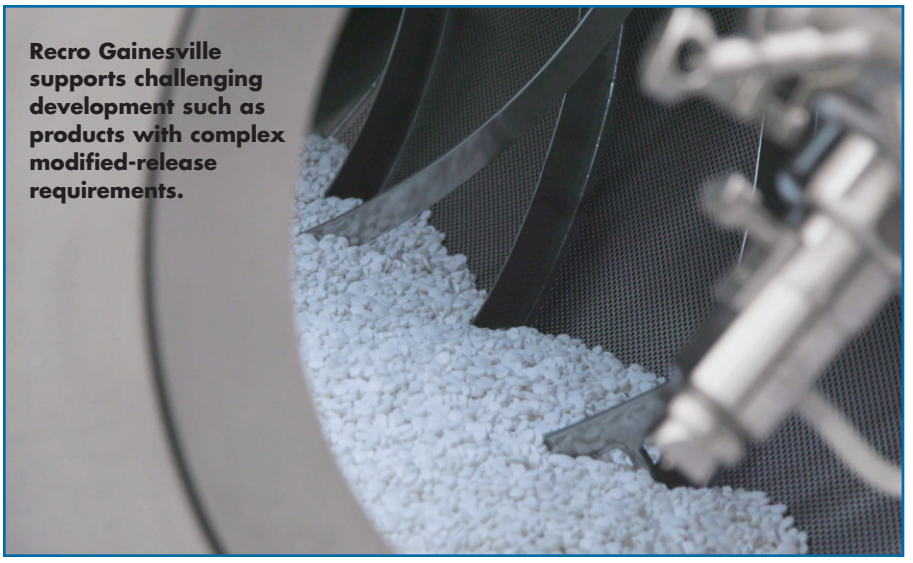
PCI transferred the existing processing parameters using a specifically designed mathematical scaling model. "We performed a full Design of Experiment (DoE) program with the aim of investigating the critical processing parameters on the influence of the assay and content uniformity results," she explains. "Eight experiments were conducted and analyzed alongside a review of the data from the previous CDMO. We identified a number of variables and the DoE analysis indicated that the assay value and content uniformity would be more desirable if high spray rate was avoided at low atomizing pressure."

As a result, the robustness batches were manufactured using the optimized design space identified during the DoE experiments with the batches confirming the statistical design space. The newly developed processing parameters were translated into master batch records for clinical Phase 2 studies. "The favorable results meant we were able to scale up the batch size and proceed to Phase 3, validation, and subsequent commercial supply on behalf of the client," she says.

Recro Gainesville: Managing Challenging Molecules From Early-Stage Feasibility to Commercialization

As a CDMO with expertise in oral solid dosage pharmaceuticals, Recro Gainesville is most often asked to tackle formulation and process development for tablets or capsules ranging from benchtop feasibility through clinical supply manufacturing or technical transfer. Often, these projects are challenging because they include specific combinations of special needs such as modified release, solvent processing, multi-step processes, and/or involve controlled substances, explains Richard Sidwell, PhD, Vice President and Chief Scientific Officer, Recro Gainesville. "In the past few years, there has been a trend towards more complex formulations involving multiple intermediate steps. Fixed-dose combinations and modified-release dosage forms with unique release profile requirements are becoming more common," he says. "For example, we have received multiple inquiries for fixed-dose combinations in which the release needs to be controlled for one or both APIs, often with slightly different release characteristics.

In addition, Dr. Sidwell says the



Recro Gainesville supports challenging development such as products with complex modified-release requirements.

CDMO has seen more early-stage feasibility work for challenging molecules. Developing an early understanding of the API (and later the formulation and the process) ultimately leads to positive outcomes during scale up and generates a knowledge database to address questions that may arise during investigations or review. "The early-stage feasibility work may include pursuing multiple delivery strategies or identifying an optimal trade-off between drug delivery optimization and processing complexity," he says.

Having clients start with Recro for early drug product development studies and stay with Recro through clinical supply manufacturing and commercial launch remains a central focus of the CDMO. Dr. Sidwell says: "Building relationships with clients during early development work and then continuing into later phase manufacturing not only promotes technical (i.e. process knowledge) continuity, but also supports development of a robust regulatory filing strategy."

Understanding the filing requirements and strategies at different phases of development can help create a more streamlined development path overall, he adds. "Without an understanding of regulatory requirements for an NDA, it is easy for early success in the clinic to lead you far down the development pathway without maintaining sufficient CMC support in terms of materials, formulation, and process understanding," he says. "Once the shortcomings of the CMC development package become apparent, it can be expensive and time-consuming to step back and rectify, particularly when the pressure is on to file ASAP. A strong understanding of regulatory requirements and a forward-thinking approach can help avoid the risks of late-stage problems or dead-ends that might lead to a need for repeat clinical work."

Singota Solutions: Capabilities Tailored to Specific Client Needs

At Singota Solutions, robotic aseptic filling is done in a completely gloveless workcell, providing repeatable precision fills with reduced particulate counts versus conventional technology, claims Ken Chomistek, Director of Quality Control and Development at Singota Solutions. "Our gloveless robotic filling isolator allows us to take a formulation from project inception to filled units in a few short months versus nine months (or more) by other CDMOs," he says. "Our system is ideally suited for the production of clinical and niche commercial injectable products in vial, syringe, and cartridge formats."

Singota's manufacturing facility can handle a range of small-molecule and biological formulations, including potent compounds. Mr. Chomistek says that Singota witnessed an increased interest from clients for small quantity batch filling for both vials and prefilled syringes of parenteral formulations. "Being able to aseptically manufacture 500-10,000 units in a couple months can save money, time, and can provide a first to clinic advantage over competition."

The Vanrx SA-25 Robotic Fill Workcell at Singota Solutions can manufacture 500-10,000 units in a matter of months.

"As companies work on drugs for smaller patient populations, the reduced quantities of drug material required during the clinical trial process potentially means a more simplified supply chain and the sponsor company no longer has to manage multiple CDMOs as in the past," – James E. Cherry, Vice President, General Manager, Cambrex.

As an example, he explains how Singota worked with a client to design dosing studies for its product. "Initially, they had a vial that required clinicians to measure patient dosing for each injection. We helped optimize small-volume fills in prefilled syringes — as an alternative to the vials — to reduce potential errors in the clinic."

Manufacturing at Singota goes hand in hand with formulation development, which Mr. Chomistek states is a 'simple is better' approach. "Our clients want more efficiency out of their excipients," he says. "If a single excipient can have multifunctionality, it can keep the formulation simpler and easier to manufacture and test down the road. As a result, clients are regularly challenging us to help them to find, evaluate, and report on new excipients and their multifunctionality."

Dr. Reddy's Custom Pharma Services: Starting With the End in Mind Mitigates Risk

Custom Pharma Services (CPS) at Dr. Reddy's is a one-stop-shop CDMO, delivering 170-plus projects and working with more than 200 customers globally. CPS supports pharmaceutical companies across the value chain of development to commercial manufacturing; from intermediates and drug substances to drug product formulations.

"Extensive understanding of regulatory requirements for INDs, clinical phases, and NDA filing programs enables CPS to customize product solutions as 'fit-for-purpose,' says Rashmi Nair, Technical Manager-Business, Dr. Reddy's. "With state-of-the art R&D and GMP facilities that are inspected by stringent regulatory authorities, best industry practices for documentation through electronic note books and a range of technologies, services, and scales of operation, CPS ensures time and cost-effective product solutions."

CPS adopts a 'start-with-the-end' approach and considers formulation as the eventual deliverable of any drug development program irrespective of the scope of project: intermediates, API or formulation. This approach helps envisage risks, required precautions, and commercial viability, and support customers with a partner approach, not as a mere service provider, says Ms. Nair. This approach benefited a small biotech in Europe. The customer approached CPS for process development of the API, an anti-infective high dose drug. It was for a clinical Phase 2 program. The API process required chemical synthesis, conversion to amorphous solid by spray drying, and then a granulated blend filled in sachets as a formulation. This process was an 8-day activity at the API stage and a 3-day activity at formulations, with frequent issues in powder flow during sachet filling. Ms. Nair says the CPS team proposed a process simplification approach with *in-situ* amorphization and particle design in a manner that modified API micromeritcs-generated densified material for formulation. With customer approval, a proof-of-concept was established utilizing process analytical technology such as Focused Beam Reflectance Measurement and Particle Vision Measurement, and gram scale prototypes. "With close coordination of the API and formulation teams, a go-to-market product was developed," she says. "Today the drug program is in clinical Phase 3 and utilizes this new process, saving the customer about 27% more cost and 35% more time than the original process."

Almac Pharma Services: Flexibility to Meet Varied Client Needs

According to John McQuaid, Vice President Technical Operations, Almac Pharma Services, there are two key benefits to working with a full-service CDMO: efficiency and continuity. "We streamline the transfer of goods as they move from drug substance development and manufac-

ture to drug product development and manufacture, then on to clinical packaging," he says. "This saves valuable time in the overall clinical supply chain."

Mr. McQuaid says that a full-service CDMO like Almac also streamlines the transfer of know-how at each step, with interdisciplinary teams that share expertise across the transitions. "Clients benefit from having one highly skilled technical team capable of developing the formulation and analytical method in-house, then carrying it through to clinical trial material manufacturing, scale up, and ongoing commercial supply. In short, we ensure that product-specific knowledge gained over several years is maintained."

One area in which Almac has specific knowledge is in pediatric formulations, which has increased in interest over the past year, says Mr. McQuaid. "The increased interest in pediatric formulations is driving a demand for powder-in-bottle, mini-tablets, and stick packs. API-in-capsule using Capsugel's Xcelodose® technology remains popular, and clients have expanded their use of it from Phase 1 clinical trials into Phase 2 and beyond."

One Almac client had a commercialized adult dosage form that needed a corresponding pediatric dosage form with multiple dosage strengths in an easy-to-use packaging format. Mini-tablets filled into stick packs were identified as the best presentation. "Mini-tablet development differs from standard tablet development," says Mr. McQuaid. "Nevertheless, Almac successfully optimized several equipment features: punch tip concavity; ejection scraper design; ejection cam position; and punch and turret keyways. We also custom-designed 37-tip punches that allowed compression rates up to 550,000 mini-tablets per hour. We customized a packaging solution as well. In conjunction with a third-party specialty vendor, the team successfully identified, installed, and qualified stick-pack filling equipment."

In addition to pediatric formulation knowledge, Almac has regulatory experience to handle complex drug products. "As products become more complex and the regulatory requirements becomes more exacting, clients are looking to us to shoulder more of the burden," he explains. "On the front end, our documentation can be dropped easily into clients' regulatory submissions with little editing. We have also drafted entire sections of clients' submissions on their behalf. On the back end, our quality and regulatory experts work with clients to ensure smooth and successful inspections."

Almac is also being asked to take on commercial supply of clients' products, often at, or close to, the same scale provided for clinical studies. This, says Mr. McQuaid, is occurring as there is an industry trend toward higher value, lower volume products. "Our production facilities span pilot to large scale, so we've had success meeting our clients' increasingly varied demands."

This flexibility is how Mr. McQuaid says Almac differentiates itself from other CDMOs. "Once we understand our clients' objectives, we can customize the best business solution. For example, traditional fee-for-service relationships still work for some of our clients, but for many others, a more strategic partnership is preferable. In those instances, they may opt to secure dedicated capacity, equipment, or GMP floor space to meet their business demands."

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BIOGRAPHY

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

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MARKET BRIEF

Nothing Degrading About Saving Lives: E3 Ligands Recruiting New Drugs Into the Clinic

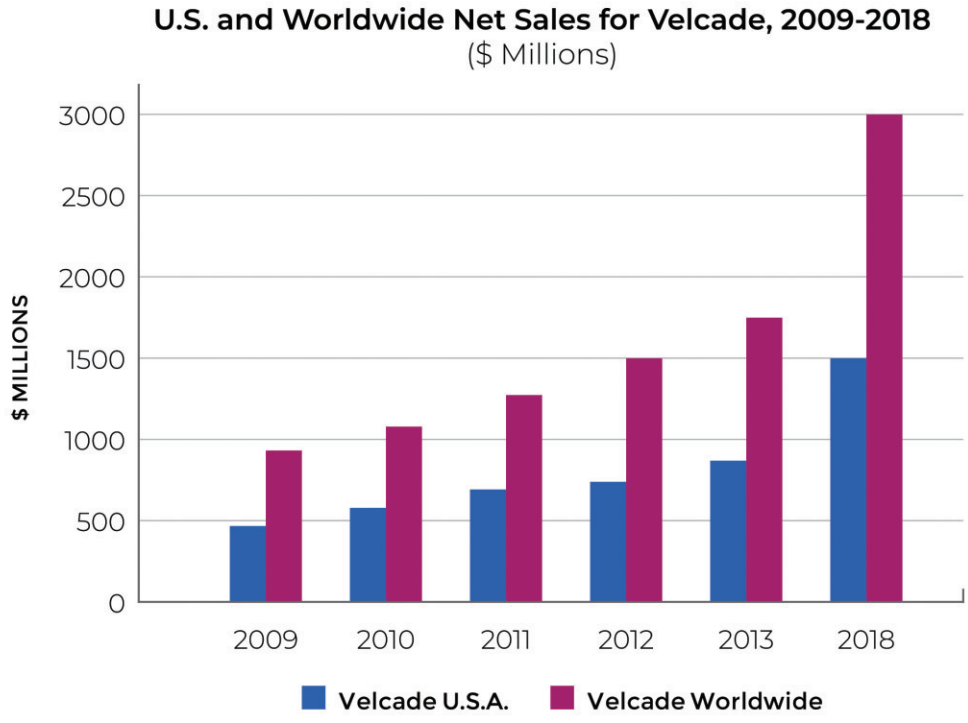
By: Marianna Tcherpakov, PhD

INTRODUCTION

The Ubiquitin Proteasome System (UPS) represents one of the most studied and challenging areas in basic and applied science. Indeed, the scientists who discovered this cellular phenomenon were awarded the prestigious Nobel Prize in Chemistry in 2004.

Since 2004, ubiquitin ligases and proteasome function have become one of the major targets for pharmaceutical and drug discovery companies. However, further development in this sector remains challenging. E3 ligases have been long regarded as "undruggable targets." Despite these failures both scientifically and financially, humiliations did not fully disrupt intense research efforts that persisted due to the enormous potential upside. Here, we discuss underexploited strategies, traditional approaches that can be optimized, novel techniques beginning to emerge and pay dividends, and results propelling this field toward better clinical outcomes. Targeted protein degradation (TPD) in particular, is renewing optimism in what was at one stage a field drowning in

FIGURE 1



"This represents an entirely new rationale in the way proteins are targeted: instead of relying on small molecules that bind to druggable targets, such as enzymes, ion channels, and receptors (representing 10% to 15% of cellular proteins), TPD offers a unique means to unlock the remainder of the proteome, including previously undruggable proteins, such as transcription factors and scaffolding molecules."

garbage proteins.

The main reason for that is complexity of the system and requirement for reliable well-established assay platforms to develop therapeutics. The ubiquitin-proteasome system plays a central and essential role in regulating protein homeostasis in mammalian cells. There is a complex multistep process involving the polyubiquitination of proteins prior to their proteolytic degradation by the 26S proteasome complex. Overall, protein ubiquitination occurs through a cascade of enzymatic reactions, involving an E1 ubiquitin-activating enzyme, an E2 ubiquitin-conjugating enzyme, and, finally, an E3 ubiquitin-ligase enzyme complex. Repeated iterations of this ubiquitination process result in long chains of ubiquitin repeats on a given substrate and posterior degradation by the proteasome.

Importantly, E3 ubiquitin ligases (more than 700 are known in humans) confer substrate specificity to the protein ubiquitination pathway, making this enzyme a very attractive target for specific and less toxic therapeutic treatment, reducing side effects that can be related with other UPS components, such as proteasome inhibitors.

Indeed, proteasome inhibitors (Velcade as an example) became huge blockbusters with billions of dollars in annual sales (Figure 1). Second-generation inhibitors also brought substantial amount of revenues.

Although Velcade is a successful drug for multiple myeloma treatment, it still has a lot of side effects. Because the compound affects protein degradation pathway in general, scientists are looking for more targeted approaches in drug development. Thus, targeting E3 ligases that by definition degrade specific cellular targets seems to be more logical.

However, despite extensive research (structure, function, localization, and regulation), E3 ligases still didn't make it big in drug development market: the development of small molecules against E3 ligases has been rewarded with very limited success, leading to the idea that they are undruggable targets.

As of today, three compounds (thalidomide, pomalidomide, and lenalidomide) targeting the E3 ligase Cereblon have been approved for the treatment of multiple myeloma or mantle cell lymphoma, and only a handful of compounds targeting the XIAP E3 ligase, IAP, and the MDM2 E3 ligase have entered clinical trials. Additional research efforts have focused on targeting other E3 ligases, including Skp2, βTrCP, Fbox3, VHL, and Parkin. However, there is a significant difference between the number of E3 ligases and the number of drugs in clinical trials or approved. Overall, it can be considered that the field is still very much in its preliminary stage.

So, why does the development of novel E3 ligase molecules remain a relatively unexploited source by pharmaceutical industry? The answer is that the general biology and chemistry of the E3 ligases is very complex. Moreover, linking individual E3 ligases to their substrates is an essential precursor step. This relies on either a functional connection or a physical association between proteins. However, biochemical screens have proven not to be effective to identify E3 substrates, as the binding between E3 ligases and substrates is often intrinsically weak.

In summary, more knowledge is required on the biology and mechanism of E3 ligases, their substrates, and finally how they link to diseases in order to increase the success of future drug discovery entrepreneurships.

TARGETED PROTEIN DEGRADATION & PROTACS- THE MOST POPULAR TREND OF UPS DRUG DISCOVERY

There is a novel approach to target and dispose of troublesome proteins, and it is creating huge interest in the drug development industry.

The emerging modality, known as targeted protein degradation (TPD), uses a bifunctional chemistry to create chimeric molecules that bind to a protein of interest while simultaneously tagging it for degradation via the cell's own proteolytic machinery.

This represents an entirely new rationale in the way proteins are targeted: instead of relying on small molecules that bind to druggable targets, such as enzymes, ion channels, and receptors (representing 10% to 15% of cellular proteins), TPD offers a unique means to unlock the remainder of the proteome, including previously "undruggable" proteins, such as transcription factors and scaffolding molecules.

Proteolysis-targeting chimeras (PROTACs) are bifunctional molecules designed to recruit an E3 ubiquitin ligase to a specific target protein, thereby providing a mechanism to ubiquitinate and degrade specific pathological proteins.

A significant body of preclinical data, generated since PROTACs were first introduced 15 years ago, demonstrates that PROTACs provide a robust approach to expose new cell biology and to generate novel therapeutics with the potential to target currently undruggable proteins. PROTAC technology has a number of advantages:

- Like small molecules, PROTAC molecules possess good tissue distribution and the ability to target intracellular proteins.
- PROTACs can degrade proteins regardless of their function. This includes the currently "undruggable" proteome, which comprises approximately 85% of all human proteins.
- They have the ability to target overexpressed and mutated proteins, as well as the potential to demonstrate prolonged pharmacodynamics effect beyond drug exposure.
- Due to their catalytic nature and the pre-requisite ubiquitination step, exquisitely potent molecules with a high degree of degradation selectivity can be designed.

However, in practice, engineering bifunctional molecules that can effectively bind a protein target and an E3 ubiquitin ligase in sufficient proximity is not so trivial. The rules of this process are still being understood and often combine prior knowledge of a protein's structure and function with high throughput chemical platforms. Proteins of interest (the protein to be degraded and the E3 ubiquitin ligase) are interrogated with small molecule libraries to identify binders that can then be joined in such a way that a permissive complex is formed, enabling ubiquitination of the target protein.

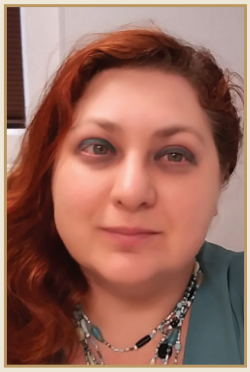
Although TPD/PROTACs can help with many of the drawbacks of small molecular drugs, it has also challenges that need to be addressed. One concern is understanding the biological consequence of effectively knocking-out a protein from a cell that might well have multiple functions.

Another obstacle is finding ways to deal with the size of these bifunctional molecules, and the impact this has on metabolic stability and delivery routes. The size of small molecule inhibitors is typically in the range of 300 Da to 500 Da, while TPDs range from 700 Da to 1000 Da. One concern is that this might affect the oral availability of TPDs.

Despite those disadvantages, many believe that PROTAC technology will revamp UPS drug discovery and development introducing new approved drugs into market in the next couple of years. ◆

This executive summary is based on the following market research report published by BCC Research: E3 Ligands Recruiting New Drugs (PHM192A). For more information, visit https://www.bccresearch.com.

BIOGRAPHY



Dr. Marianna Tcherpakov has more than 10 years of experience as a bench scientist specializing in the areas of biochemistry, cell biology, and industrial assay development and drug manufacturing. She has contributed to a number of scientific publications and holds several patents. She has expertise as an assay development scientist and is familiar with different research field trends and likely future developments. She earned her MSc in Science Management from NYU and her PhD in Molecular Neurobiology from Weizmann Institute of Science in Israel.

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Drug Development
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Martine Dehlinger-Kremer, PhD
VP, Pediatric Development
Synteract

Synteract: Advances in Pediatric Clinical Research & The Promise for the Future

While the pediatric use section to the label template was established in the US as early as 1979, and the FDA began further initiatives to improve pediatric-use information on drug labeling with the first of several rules in 1994, many medications still lacked prescribing information for children and had not been tested and evaluated for them. Today, increasing legislation in the US and the EU makes pediatric development plans a requirement for all new medicines that do not have a waiver or are exempt from pediatric regulations, not just those that are specifically for children. What does this mean for drug developers, young patients, and their families?

Synteract is a CRO that has been at the forefront of working with sponsors in pediatric clinical research, with 260+ pediatric clinical projects conducted globally. In November 2018, it acquired KinderPharm, a pediatric specialist CRO, to further build out its pediatric drug development offering. *Drug Development & Delivery* recently spoke with Dr. Martine Dehlinger-Kremer, Vice President, Pediatric Development at Synteract to discuss current and significant challenges in pediatric clinical research, advancement of regulations surrounding them, and where the industry is headed.

"Although consent by parents/guardians is a legal requirement for trials, the explicit wish of children must also be respected, and investigators need to include them in decision-making as much as they are capable, depending on age and mental maturity. Information about the trial should be provided in an age-appropriate format to improve comprehension, show respect, preserve trust, and enable cooperation."

Q: What are some of the biggest challenges when it comes to pediatric clinical trials compared to other types of clinical trials?

A: Pediatric clinical trials are still not as well accepted by society. Even today, more than 50% of medicines administered to children have never been tested in this population, yet there is still some reluctance about involving children in trials, particularly by parents and some physicians. They fear harming young patients due to uncertain treatment effects, or that their ailing child may be administered a placebo. Investigators are apprehensive to recruit children for trials given the large amount of information they must provide to families and the trial participants. Work still needs to be done to help investigators understand families' perceptions of trials and how to best provide support and improve recruitment.

Participation in trials is improved by having trained investigators who understand the complexities, appropriate facilities that meet the needs of children, and experienced trial coordinators to facilitate recruitment and trial conduct. It is important to have an appropriate child-friendly environment and to adapt treatments to their special needs. Trials should be as pragmatic and flexible as possible, with limited additional testing and monitoring beyond requirements of routine clinical care. Visits should be scheduled around school hours and holidays as much as possible. Having nurses go to the home of the child for some tests to avoid visits on site may help as well.

The importance of engaging families in trials design, review of protocols, and patient-facing documents cannot be underestimated. One way to help parents and children decide to participate in a trial is by improving readability of the consent and assent. Using plainspoken, clear documents that are more graphical in nature for younger age groups along with videos, infographics, or pictures to explain the clinical trial will effectively help orient families and children.

Finally, the burden of trial participation is different for children versus adults. For example, some children's fear of needles may make obtaining blood samples challenging. To address this burden and protect children from unnecessary testing, one should consider trial designs with sparse sampling that minimize the number of required blood draws. It is also advised that the volume of blood taken be limited in children, and especially in those that are younger. Hence, the volume of blood sampling allowed in pediatric trials is less than 3% of the estimated circulating blood volume over a period of 4 weeks and should not exceed 1% at any single time. Alternative appropriate sampling techniques, such as finger or heel pricks or salivary samples, may be preferred as they minimize discomfort. Also, specific assays, such as micro-assays, are critical for pediatric trials as they allow analysis with limited blood amounts.

Q: When it comes to the pediatric population, infants obviously have different needs than toddlers, grade-school age children, or preteens. How can the industry address the different needs of pediatric age groups in clinical trials?

A: The pediatric population is indeed not a harmonized population. It is advisable to have the protocol and patient-facing documents, such as the assent form, reviewed by patients/advocacy groups before implementation to ensure they are adapted to the child's age and maturity level.

We recommend providing tailored trial information on

aspects important to parents. Parents or guardians must be allowed enough time to make a decision, taking into consideration the amount and type of information provided, organization of the consent meeting, communication style, and additional materials (e.g., illustrated booklets, videos) provided.

Although consent by parents/guardians is a legal requirement for trials, the explicit wish of children must also be respected, and investigators need to include them in decision-making as much as they are capable, depending on age and mental maturity. Information about the trial should be provided in an age-appropriate format to improve comprehension, show respect, preserve trust, and enable cooperation. Children's dissent must be respected, particularly if it is different from their usual response to similar procedures in normal clinical care. If the child refuses to participate, the investigator cannot include them. If the investigator cannot convince him/her, regulations and ethics guidelines will not allow their inclusion.

Q: Has the industry progressed when it comes to recruitment of pediatric populations?

A: The industry and regulators are working together to improve pediatric research and ensure medicines are adequately developed. Pediatric networks are being created to facilitate clinical trials in children. International pediatric trial networks have been established to improve infrastructure and research. The US and EU created networks with specialized expertise in conducting trials in children and have dedicated funding for pediatric research and training.

The National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) in the UK was established in 2005. This network, which benefited from government funding, has been very successful. By 2012, 25,000 children were recruited to over 300 Medicines for Children Research pediatric trials.

The US Pediatric Trial Network (PTN), sponsored by Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), was launched in September 2010 for a 7-year program, with $95 million to conduct pediatric trials on off-patent medicines. This network provides an appropriate environment for performing safe and effective trials in children as recommended by the Best Pharmaceuticals for Children Act (BPCA), a drug development program in a variety of therapeutic areas. In 2012, the network, in collaboration with the FDA, commenced pediatric studies on 30 drugs. As of today, PTN recruited over 7,000 children in 38 studies.

The Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) was established in March 2011 in collaboration with research networks, investigators, and centers with recognized expertise in conducting pediatric trials. This network is working toward developing necessary competencies and avoiding unnecessary duplication of pediatric studies, educating parents or caregivers and children about trials and encouraging their participation, raising awareness about the necessity for trials in children of all ages with healthcare professionals, supporting their involvement in such studies, and engaging in dialogue with ethics committees on pediatric trial issues. (Note: Dr. Dehlinger-Kremer is an observer Member of the Coordinating Group of Enpr-EMA.)

I-ACT, the Institute for Advanced Clinical Trials for Children, established by Critical Path Institute in March 2017, was launched in the US to optimize and accelerate biomedical innovation using child-centered clinical trial networks and collaboration with like-minded institutions, trial sponsors, and other stakeholders.

The conect4children (c4c) project in the EU was launched in May 2018. It is a large collaborative pediatric network that will facilitate development of new drugs and other therapies for the pediatric population in Europe. The c4c consortium aims to enhance the competitiveness of Europe as a critical region for developing medicines for children by using existing expertise, patient access, and developing common processes to be applied to disease natural history studies, registries, studies of new therapies, and comparisons of existing therapies.

Patients and parents are also more involved in pediatric research. There are international children advisory groups, such as the International Children's Advisory Network (iCAN). A worldwide consortium of children's advisory groups, iCAN is dedicated to giving children and families a voice in health, medicine, research, and innovation by increasing education

about the importance of children's involvement. With chapters across the US and worldwide, iCAN (of which I am a member of the External Advisory Board since October 2018) works with CROs like Synteract and partners with local children's hospitals to help address the needs of pediatric clinical research and healthcare and advocates for patients worldwide.

Q: When it comes to the advancements for pediatric drug development, what has been successful in moving the industry forward and what has not?

A: Pediatric regulations in the US, including BPCA, PREA, and FDASIA have been successful. In the US, drugs with Orphan Drug Designation were exempt from PREA requirements. With the FDARA from 2017, and the RACE for Children Act, this exemption will be eliminated for cancer drug development, and therefore, will improve opportunities for children by:

- Ending exemption of PREA obligations for cancer drugs with orphan designations if the molecular target of the drug is relevant to children's cancer
- Requiring companies to evaluate their product in children when the molecular target of their drug is relevant to children's cancer

Even though the Pediatric Regulation entered into force much later in the EU than in the US, Europe has had great success in adding new drugs approved for children as well as new indications for children. There is, however, still some room for improvement as not all PIPs are completed on time.

In the EU, the 10-year Commission report on EU Pediatric Regulation (October 26, 2017) recognized the positive impact of the Pediatric Regulation overall, though the Regulation appears most effective when adult and pediatric needs overlap. Fewer advances have been made in diseases that are unique to children. While some instances of over- or under-compensating drug developers with financial rewards exist, overall benefits appear to outweigh costs.

Therefore, the European Commission does not currently recommend re-opening the legislation. It will evaluate pediatric and orphan regulations to better understand why rewards do not seem to be driving development for rare childhood diseases. Findings are expected to be delivered in 2019, enabling the next Commission to make informed policy decisions.

Meanwhile, the European Commission and EMA have started to streamline application and implementation of the Regulation, including making changes to deferrals and revisiting PIP processes.

A revised and revoked class waivers list has been in force since July 28, 2018. Applications for new medicines or variations of marketing authorizations will be validated against it. Waivers, specifically in oncology, will no longer be automatic. Regulators will expect companies to have considered product mechanism of action and pediatric needs prior to decision.

The EU Commission and EMA held a workshop with patients, academia, healthcare professionals, and industry on March 20, 2018 to discuss potential improvements to the Regulation. An action plan, taking into account recommendations collected during the workshop was published in October 2018. The action plan is structured around five topics areas:

- Identifying pediatric medical needs
- Strengthening of cooperation of decision makers
- Ensuring timely completion of pediatric investigation plans (PIPs)
- Improving the handling of PIP applications
- Increasing transparency around pediatric medicines.

The action plan, that consists of 21 actions in total, should address the challenges identified by the EU Commission and EMA and increase the efficiency of pediatric regulatory processes in the current legal framework and boost the availability of medicines for children. The completion of this action plan takes into consideration the Brexit, EMA relocation, and business continuity plan. Some actions are deferred and some deadlines are likely to be revisited. The completion of all the actions is thus not expected within the initially planned 2 years time frame, i.e., by the end of 2020.

Close collaboration between the US and the EU has improved pediatric clinical research significantly. We look forward to continued oversight and the resulting benefits to children, who need these medicines, and their families. ◆

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IN VITRO DDI STUDIES

2017 FDA Guidance: Many In Vitro DDI Evaluations Should Precede FIH Studies

By: Brian Ogilvie, PhD, and Andrea Wolff

INTRODUCTION

In October 2017, the FDA released its much-anticipated draft guidance documents for drug-drug interaction (DDI) studies — and changed the recommended timing of these evaluations. Even before then, we had an inkling of what was to come. As early as summer 2017, a client about to enter Phase 1 development for an oncology drug received a request from the FDA. The agency requested that our client add restrictive exclusion criteria to the first-in-human (FIH) clinical protocol for numerous co-medications that were possible substrates of the major drug transporters. At the same time, the FDA suggested that the sponsor could avoid these exclusions by providing *in vitro* transporter and reaction phenotyping data prior to the FIH clinical study.

While the new guidance contains many important changes — notably, amended cutoff criteria and safety factors for the basic inhibition study models — the earlier timing of DDI studies is, perhaps, the most daunting.[1] This is especially true for developers with drugs in the later clinical stages. Does this guidance mean sponsors are required to backtrack, and if so, how far? This article outlines the implications of these new timing requirements and best practices for negotiating them efficiently and effectively moving forward.

WORKING BACKWARD FROM THE CLINICAL GUIDANCE

In response to commentary on the 2012 guidance regarding its navigability, the 2017 guidance is organized as separate *in vitro* and clinical documents. It is Section III of the clinical document (Table 1) that speaks to the timing of *in vitro* DDI studies. Because of its pertinence and subtlety, the section is reproduced here, verbatim.

TABLE 1

Study Type	FDA	PMDA
Victim: Metabolite ID and phenotyping	*Before* phase I	
Victim: P-gp & BCRP substrate potential	*Before* phase I	
Victim: Other transporter substrate potential	Early as possible based on routes of elimination	
Perpetrator: CYP inhibition & induction	*Implied* before phase I	*Before* phase I
Perpetrator: Transporters	*Before* phase I	

Timing was also covered for some studies in the 2013 EMA Guideline on the Investigation of Drug Interactions

"The guidance indicates that failing to characterize the potential for DDI before FIH studies may result in undesirable conditions being placed on the drug to ensure patient safety: restrictive labeling, post-marketing requirements, or commitments and delayed approval. Furthermore, the guidance notes that sponsor plans for determining the DDI potential of a drug candidate will be a topic of discussion at milestone meetings with the FDA; drug developers must be prepared to present regulators with robust strategies for early, in vitro DDI evaluation, taking into consideration the indication and likely co-medications."

CLINICAL DRUG INTERACTION STUDIES — STUDY DESIGN, DATA ANALYSIS, AND CLINICAL IMPLICATIONS

USFDA Draft Guidance for Industry, 2017 – Timing of Clinical DDI Studies

"After conducting in vitro drug metabolism and drug transporter studies, sponsors should determine the need for and timing of clinical DDI studies with respect to other studies in their clinical development program. Sponsors should evaluate DDIs before the product is administered to patients who are likely to take concomitant medications that could interact with the investigational drug. Furthermore, sponsors should collect enough DDI information to prevent patients from being unnecessarily excluded from any clinical study because of their concomitant medication use. Unnecessary restrictions on patient enrollment can result in clinical study populations that are not representative of the indicated patient population. Inadequate studies of DDIs can hinder the FDA's ability to determine the benefits and risks of an investigational drug and could result in restrictive labeling, postmarketing requirements or commitments, and/or delayed approval until sufficient information on DDIs is available. Sponsors should summarize their DDI program at milestone meetings with the FDA. Potential discussion topics at these meetings include the planning, timing, and evaluation of studies to determine the DDI potential of the investigational drug."

The guidance states that sponsors should determine the timing and need for clinical DDI studies after conducting *in vitro* drug metabolism and drug transporter studies and before the drug is administered to patients taking interacting medications. *In vitro* studies elucidate the potential for DDI. The goal is to collect enough DDI information to prevent patients from being unnecessarily excluded from the study, thus keeping study populations more representative of relevant patient populations to better define patient safety — with the added benefit of expediting enrollment.

The guidance indicates that failing to characterize the potential for DDI before FIH studies may result in undesirable conditions being placed on the drug to ensure patient safety: restrictive labeling, post-marketing requirements, or commitments and delayed approval. Furthermore, the guidance notes that sponsor plans for determining the DDI potential of a drug candidate will be a topic of discussion at milestone meetings with the FDA; drug developers must be prepared to present regulators with robust strategies for early, *in vitro* DDI evaluation, taking into consideration the indication and likely co-medications.

In summary, neglecting to address DDI before clinical studies may impede your program progression.

MAKING ASSUMPTIONS WITHOUT CLINICAL DATA

Testing for definitive *in vitro* DDI data, including metabolism and transporter data, early in the development process is a major departure from recent practice. In the past, sponsors would consider the clinical program, decide which aspects needed to be de-risked, and perform appropriate studies in the FIH to proof-of-concept stage, or even as late as Phase III. Now, these data will frequently need to be obtained in the absence of any clinical data.

But without the results of single or multiple ascending dose (SAD/MAD) studies, what drug concentration should be tested? Lines 812-815 of the *in vitro* guidance sug-

gest that concentrations should be as high as possible, limited only by solubility and cytotoxic effects on cell models. By using the maximal concentration, developers will produce data applicable to the widest range of clinical dosages possible. Some contract research organizations (CROs) have developed strategies to handle this situation.

Obtaining such broad-spectrum *in vitro* data does have clinical stage benefits. Should indications or formulations be amended as the program develops, such that the Cmax must be raised above that in the SAD/MAD studies, the *in vitro* data will be ready to support the new dosages, averting the need to repeat definitive studies at a later date.

BUT THESE ARE JUST DRAFT RECOMMENDATIONS, NOT REQUIREMENTS, RIGHT?

The short answer to this question is: Wrong. The good guidance practices regulations (21 CFR 10.115), which were revised in April 2017, address whether guidance recommendations are requirements.[2] Technically, no, they are not. However, the regulations go on to explain that guidances, "represent the agency's current thinking … FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence." In other words, in the absence of a very convincing reason, sponsors are expected to follow guidances.

In addition, the fact that the guidance is just a draft should be ignored. The aforementioned regulations further state that the "FDA also can … review any comments received and prepare the final version of the guidance document that incorporates suggested changes, when appropriate." In other words, the FDA can, but is not required to, issue a final version. Because neither the 2006 nor the 2012 guidance was finalized, waiting for the final 2017 guidance is not sensible. The best plan is to follow the latest guidance moving forward and take all opportunities to communicate the proposed strategy to the FDA, presenting science and data, as needed, to justify any departures from current recommendations.

WHY GOOD SCIENCE IS GOLDEN

The source of all these recommendations is, ultimately, the community of scientists. Guidances are understood to be living documents — which reasonably explains the apparent reluctance to finalize them. As stated in the *in vitro* guidance's introduction (lines 29-31), the goal is to "describe a systematic, risk-based approach to assessing … and … [mitigating] DDIs." Given this purpose, as new knowledge comes to light, the guidances will need to be updated. Indeed, the FDA maintains its list of *in vitro* probe substrates on the web, for easy revision.[3] In essence, the FDA expects, or even needs, the industry to drive innovation.

This open stance is suggested in statements scattered throughout the guidance, regarding the possibility of alternatives. For example, around line 373, in the transporter section, the authors offer that alternative cut-off ratios may be justified based on a sponsor's prior experience. Further down, in the metabolite section (line 579), we find: "Alternative methods are acceptable if the sponsor can justify that the DDI potential of the metabolites can be adequately assessed."

These are clear invitations to communicate and apply the most current research results, even when they contradict the written recommendations. Doing so not only helps sponsors perform and interpret studies sensibly, but it also helps the FDA keep abreast of new scientific developments. Proper or comprehensive justification for alternatives may come in the form of a sponsor's own published, peer-reviewed data. Publications that were likely used this way are cited in the guidance, such as those referenced immediately following the metabolite statement: Callegari, Kalgutkar, et al. 2013; Yu and Tweedie 2013; and Yu, Balani, et al. 2015. Papers like these shape subsequent iterations of guidance. The corollary of this influence is that in addition to understanding the current guidance, studying the citations listed in the guidance is highly recommended as a key to understanding the logic behind the revisions.

WHAT TO DO NOW: STRATEGIES FOR NEGOTIATING THE CHANGING LANDSCAPE

The way forward, given the new recommendations, is generally to stay on the course. For those in the late clinical stages of drug development, there is no need for undue concern. It may be possible to negotiate post-marketing commitments, but the best practice is to maintain open lines of communication with the FDA.

For those with drug candidates far enough along in development to have already produced some definitive DDI data, the best plan is to perform a risk-based gap analysis. The existing *in vitro* package should be compared with the new requirements. An experienced contract research organization can provide advice and assistance in taking the appropriate actions, which will depend upon the drug's devel-

opment stage and timeline.

In some cases, existing data can simply be reinterpreted based on the new cut-off criteria. Additional *in vitro* DDI studies may also be in order, if needed, for the new drug application. Again, taking advantage of all opportunities to communicate your strategy with the FDA is the best way to save time and avoid unexpected setbacks.

WHEN TIMELINES MATTER, HELP IS AVAILABLE TO IMPLEMENT THE NEW IN VITRO DDI RECOMMENDATIONS

Among numerous revisions to the 2017 FDA *in vitro* DDI guidance, the most significant is, perhaps, the push to obtain *in vitro* DDI data early in drug development — before FIH studies. The purpose is to render subject pools that more accurately represent the relevant patient populations by minimizing unnecessary, medication-based exclusions.

Though they are referred to as recommendations, even draft guidances should be regarded as mandatory, and stakeholders will need to adapt quickly. While presentation of compelling scientific evidence can make variations acceptable, in most cases, carefully considered changes in the testing approach will be required.

Drug development is a lengthy process, and any delay can be costly. The best overall strategy for handling the updates is to keep drug candidate programs moving. Formation of clear strategies and ongoing communication with the FDA can help. An experienced CRO may have already developed plans to cover the new designs in the latest FDA guidance documents and may therefore be able to offer the greatest efficiency in adapting drug development programs to fulfill the new recommendations. ◆

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BIOGRAPHIES

Dr. Brian Ogilvie currently serves as Vice President of Scientific Consulting at Sekisui XenoTech. With more than 20 years of experience in drug metabolism, transport, and drug-drug interactions, he has written numerous expert opinions, is an author on numerous posters and publications, and an invited speaker at many conferences. He earned his PhD in Toxicology from the University of Kansas Medical Center and his BA in Molecular Biology from William Jewell College.

Andrea Wolff is the Director of Service Logistics at Sekisui XenoTech. She has more than 20 years of experience with GLP and non-GLP *in vitro* metabolism and transporter contract research studies, and currently manages several core service support teams that cover protocol writing, report writing, data processing, and project management. She is an expert consultant and invited speaker on regulatory requirements, providing guidance on which *in vitro* studies to perform. She earned her BS with a double major in Chemistry and Biology from Baker University.

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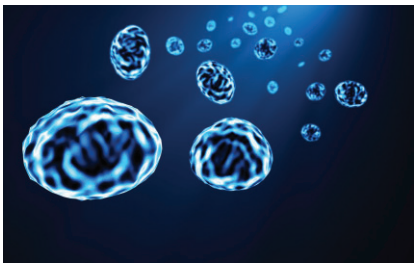

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