Drug Development & Delivery

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Accelerating Early-Stage Development

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

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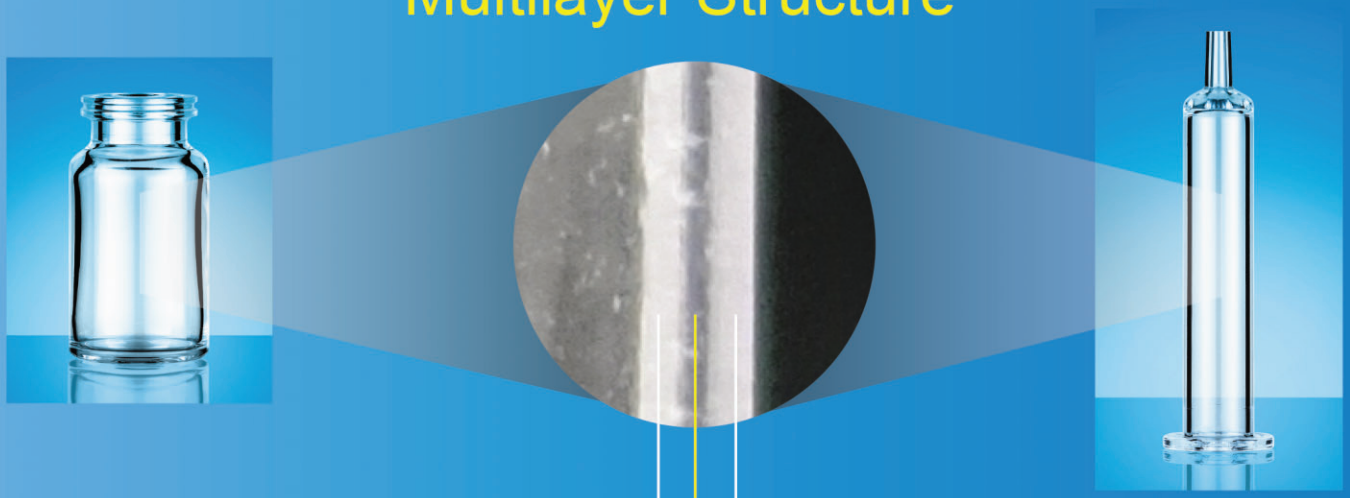

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Accelerating Early-Stage Development

"To conserve resources and get drugs to market faster, drug developers around the world are seeking new ways to make development more cost-effective and efficient. Across the industry, from virtual biotech to large pharma, drug companies are increasingly relying on outsourcing partners to access capacity and new technologies in an attempt to address these challenges and develop a competitive edge."

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"Pharma's reliance on CDMOs to provide method development, process validation, and stability storage testing has experts predicting that the global analytical testing outsourcing market will reach $9.6 billion by 2025. But they also expect that CDMOs will be challenged by more rigorous requirements put forth by pharma customers."

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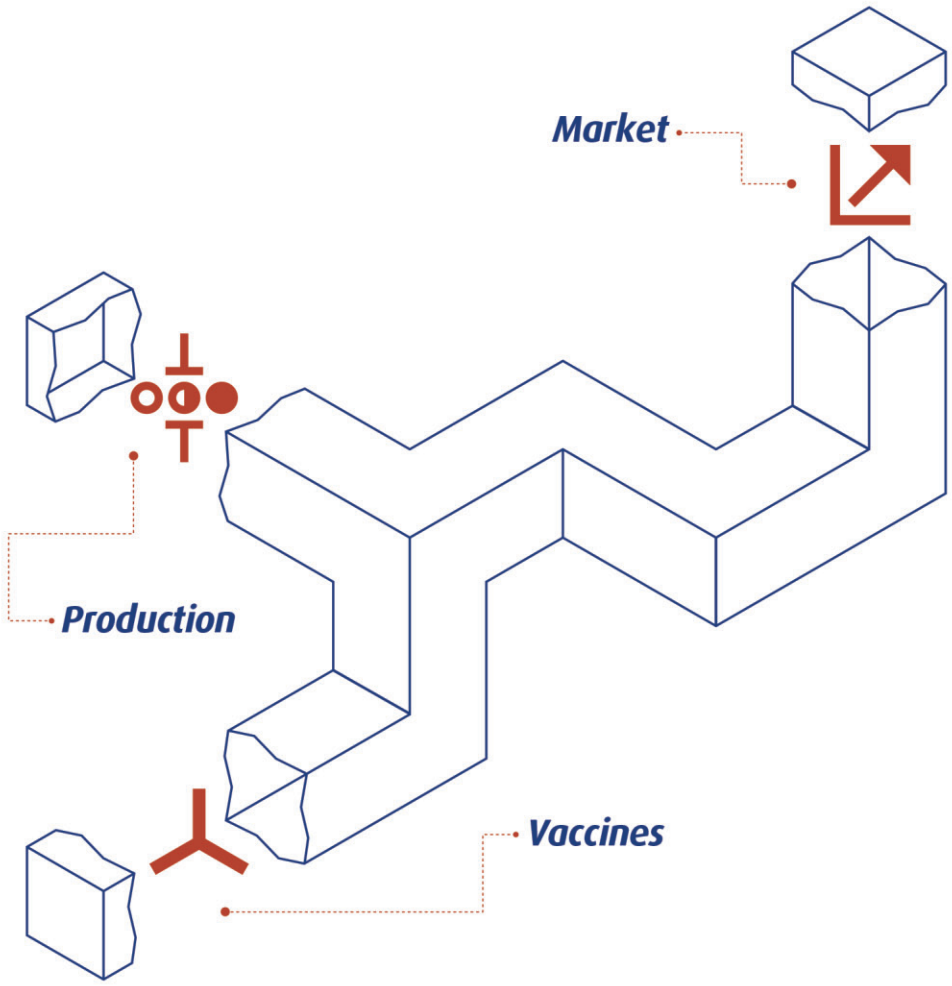
THE COMPLEX MADE SIMPLE



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BAVARIAN NORDIC

MilliporeSigma Signs Exclusive Agreement With BioDuro

MilliporeSigma has signed a supply and OEM agreement with BioDuro, LLC, on exclusive terms, for worldwide distribution of AISF ([4-(Acetylamino)phenyl]-ImidodiSulfuryl diFluoride), a convenient, shelf-stable, crystalline reagent for the synthesis of fluorosulfates and sulfamoyl fluorides. AISF was developed through a research collaboration with Pfizer Inc.

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

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

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

BioDuro is a full-service provider for integrated drug discovery and development, including discovery support, API synthesis and optimization, formulation development, and cGMP manufacture of drug products. From drug substance to drug product, discovery to development, small molecule or biologics, BioDuro is your partner for accelerating drug discovery and development and improving efficiency in establishing drug candidate success. For more information, visit www.bioduro.com.

MilliporeSigma is your trusted global partner for the development and supply of commercial quantities of functionalized PEGs (polyethylene glycols). Those in turn, are essential for your PEGylated therapeutic proteins for drug delivery. Our offerings include high-purity materials for use in investigational products in every phase of clinical development and in commercialized products. We understand that you care about rapid and cost-effective time to market. Therefore, setting the right quality attributes for the functionalized PEG is crucial for the manufacturing and stability of your PEGylated product — we can help you get it right. And during the marketing phase, expertise in life-cycle management and regulatory affairs can help you safeguard your compliance. For more information, visit www.emdmillipore.com.

SunGen Pharma Receives Its Second & Third ANDA Approval from US FDA

SunGen Pharma recently announced it has received its second and third ANDA approval from the US FDA. The second ANDA is Amphetamine Salts, a generic version of Adderall, an immediate-release tablet used to treat Narcolepsy and Attention Deficit Hyperactivity Disorder (ADHD). Amphetamine Salts had total US sales of $364 million for the 12 months ending September 30, 2018 according to IQVIA.

The third ANDA is a generic version of Deltasone, an immediate-release Prednisone product with various strengths 2.5 mg, 5 mg. Prednisone is used to treat conditions such as arthritis, blood disorders, breathing problems, severe allergies, skin diseases, cancer, eye problems, and immune system disorders. Prednisone belongs to a class of drugs known as corticosteroids. Prednisone Tablets had total US sales of $121 million for the 12 months ending September 30, 2018 according to IQVIA.

"These approvals represent two of many products being developed or co-developed by our company and with our partners around the world," said Dr. Isaac Liu, Co-Founder and Co-CEO of the company. "This is the second and third product approval for SunGen in 2018. The total number of ANDA filed by SunGen to US FDA in 2018 will be 11."

SunGen Pharma started its oral and topical research and development center in January 2016. In August 2016, it entered into a Development and License Agreement with Elite Pharmaceuticals, Inc. to collaborate to develop and commercialize four generic pharmaceutical products. SunGen formed a sales and marketing joint venture with Athenex Pharmaceutical in September 2016 named Peterson Athenex Pharmaceuticals, to market seven pharmaceutical products.

SunGen established its injectable division in October 2017 through the acquisition of a privately held pharmaceutical company based in Monmouth Junction, NJ. The company launched its first injectable product Terbutaline Sulfate as a prefilled liquid vial with a strength of 1 mg/1 ml. The product was launched July 10, 2017.

In August 2018, SunGen announced it has entered into a strategic manufacturing partnership with Grand River Aseptic Manufacturing to collaborate in the manufacturing and commercialization of generic injectable pharmaceutical products.

SunGen Pharma LLC is a privately held specialty pharmaceutical company which develops, contract manufactures, and sells pharmaceutical finished products. SunGen specializes in the development of oral solid extended release, topical and complex injectable products. SunGen has business partnerships with many North American, European and Asian based generic pharmaceutical companies to develop, manufacture, and sell several pharmaceutical products around the world. For more information, visit www.sungenpharm.com.

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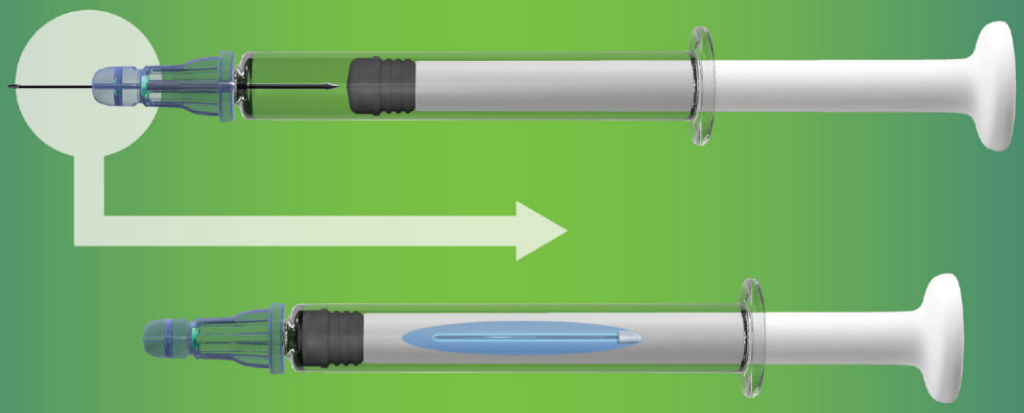

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Intensity Therapeutics Strengthens Intellectual Property Portfolio With Issuance of Several New Patents

Intensity Therapeutics, Inc. recently announced the receipt of patents protecting the company's technology and its lead product candidate, INT230-6, in China, Japan, Korea, Russia, and Australia. All five countries have granted the company a patent with multiple claims.

INT230-6, which was discovered using Intensity's proprietary DfuseRx technology platform, is composed of two proven, potent anti-cancer agents and a unique molecule that causes rapid drug dispersion throughout tumors and diffusion into cancer cells.

"We are pleased to expand our global IP portfolio with the issuance of five patents for INT230-6 in key Asian countries and Australia," said Lewis H. Bender, Founder and CEO of Intensity Therapeutics. "Cancer is the leading cause of mortality in China with nearly 3 million deaths per year and a major public health problem, underscoring the potential impact of INT230-6 and the importance of protecting our novel technology in significant global markets. We continue to prosecute patent applications in the US and countries around the world to further strengthen our IP position and secure our unique technology and treatment for solid tumor cancers."

INT230-6 is currently being evaluated in a Phase 1/2 clinical study in patients with various types of advanced solid tumors at multiple centers in the US. Intensity plans to add more North American clinical sites, as well as international sites, to the study. The company also plans to add combination arms in the study with an anti-PD-1 antibody.

As reported at the European Society for Medical Oncology (ESMO) 2018 Congress and the Society for Immunotherapy of Cancer's (SITC's) 33rd Annual Meeting, preliminary data from the Phase 1/2 study has demonstrated that INT230-6 is well tolerated with no drug-related serious adverse events or dose-limiting toxicity, indicating that INT230-6 can be safely injected, even into deep tumors. Preclinical research has highlighted the ability of INT230-6 to disperse and thoroughly saturate a tumor when administered at the proper dose-to-tumor volume ratio. In addition, preclinical data has shown INT230-6 induces a strong adaptive immune response to attack non-injected tumors and metastases.

INT230-6, Intensity's lead product candidate designed for direct intratumoral injection, is comprised of two proven, potent anti-cancer agents and a penetration enhancer molecule that helps disperse the drugs throughout tumors and diffuse into cancer cells. INT230-6 is being evaluated in a Phase 1/2 clinical study (NCT03058289) in patients with various advanced solid tumors. In preclinical studies, INT230-6 eradicated tumors by a combination of direct tumor kill and recruitment of dendritic cells to the tumor micro-environment that induced anti-cancer T-cell activation. Treatment with INT230-6 in in vivo models of severe cancer resulted in substantial improvement in overall survival compared to standard therapies. Further, INT230-6 provided complete responder animals with long-term, durable protection from multiple re-inoculations of the initial cancer and resistance to other cancers. In mouse models, INT230-6 has shown strong synergy with checkpoint blockage, including anti-PD-1 and anti-CTLA4 antibodies. INT230-6 was discovered from Intensity's DfuseRx platform.

Aravive Biologics Initiates Phase 1b Portion of Phase 1b/2 Clinical Trial

Aravive, Inc. recently announced the company has begun treating patients in the Phase 1b portion of a Phase 1b/Phase 2 trial combining AVB-S6-500 with standard-of-care therapies in patients with platinum-resistant recurrent ovarian cancer.

"We are very pleased to initiate this first trial of AVB-S6-500 in patients with ovarian cancer," said Gail McIntyre PhD, DABT, Senior Vice President of R&D at Aravive. "Our initial Phase 1 clinical trial of this agent in healthy volunteers showed a favorable safety and tolerability profile, with no reported serious adverse events and no adverse events that limited dosing in the trial. We also suppressed circulating free GAS6 across all dose levels and higher doses suppressed circulating free GAS6 for a longer duration than lower doses. We anticipate the measurement of circulating free GAS6 will be highly useful as a biomarker of drug activity in this new trial. A reduction in this biomarker has correlated to anti-tumor activity in preclinical studies."

"We are excited to have begun enrollment in this clinical trial of platinum-resistant ovarian cancer," added study investigator Bradley Monk, MD, FACOG, FACS, Professor, University of Arizona College of Medicine and Medical Director, US Oncology Research Network – Gynecologic Program. "There are limited therapeutic options for platinum-resistant patients and the GAS6/AXL pathway is known to drive progression and resistance to treatments in ovarian cancer. Agents with a favorable safety profile like AVB-S6-500 offer a great opportunity for improving outcomes for our patients."

The open label Phase 1b safety lead-in portion of the trial will enroll patients with platinum-resistant recurrent ovarian cancer and aims to confirm the dose based on results from the healthy volunteer clinical trial of AVB-S6-500. The primary endpoint for the Phase 1b portion of the clinical trial is safety, and pharmacokinetic/pharmacodynamic measurements with secondary endpoints including preliminary activity measures. The clinical trial will also explore AVB-S6-500 effects on biomarkers (GAS6-AXL) in serum and tumor tissues.

Elevated GAS6 levels have been associated with poor prognosis in cancer. As a decoy molecule, AVB-S6-500 has been shown to neutralize GAS6 activity by binding to that molecule with very high affinity. In doing so, AVB-S6-500 selectively inhibits triggering of the GAS6-AXL signaling pathway. In preclinical studies, GAS6-AXL inhibition has shown activity, whether achieved by a single agent (including AVB-S6-500) or through combinations of a variety of anticancer therapies including radiation therapy, immuno-oncology agents, and chemotherapeutic drugs that affect DNA replication and repair.

Aravive, Inc. is a clinical-stage biopharmaceutical company focused on developing innovative therapies that target important survival pathways for cancer. Aravive's lead candidate, AVB-S6-500, is a novel, high-affinity, soluble Fc-fusion protein designed to block the activation of the GAS6-AXL signaling pathway by intercepting the binding of GAS6 to its receptor AXL. AXL receptor signaling plays an important role in multiple types of malignancies by promoting metastasis, cancer cell survival, resistance to treatments, and immune suppression.

Entera Bio & Amgen Enter Strategic Research Collaboration

Entera Bio Ltd. recently announced it has entered into a research collaboration and license agreement with Amgen in inflammatory disease and other serious illnesses. Entera will use its proprietary drug delivery platform to develop oral formulations for one preclinical large molecule program that Amgen has selected. Amgen also has an option to select up to two additional programs to include in the collaboration.

"We are excited to leverage our proprietary oral drug delivery platform in collaboration with Amgen, a leader in the development of large molecule and biologic treatments in inflammatory disease and numerous other disorders," said Dr. Phillip Schwartz, Chief Executive Officer of Entera. "This collaboration is an important validation of our platform technology. Importantly, the first program included in this agreement is very different from the Oral PTH (1-34) in Entera's pipeline, highlighting the broad applicability of our technology."

Under the terms of the agreement, Entera will receive a modest initial technology access fee from Amgen and will be responsible for preclinical development at Amgen's expense. Entera will be eligible to receive up to $270 million in aggregate payments, as well as tiered royalties up to mid-single digits, upon achievement of various clinical and commercial milestones if Amgen decides to move all of these programs forward. Amgen is responsible for clinical development, manufacturing, and commercialization of any of the resulting programs.

Entera will retain all intellectual property rights to its drug delivery technology, which under this collaboration will be licensed to Amgen exclusively for Amgen's nominated drug targets. Amgen will retain all rights to its large molecules and any subsequent improvements.

Entera Bio is a clinical-stage biopharmaceutical company focused on the development and commercialization of orally delivered large molecule therapeutics for use in orphan indications and other areas with significant unmet medical needs. The company is initially applying its technology to develop an oral formulation of a human parathyroid hormone analog, Oral PTH (1-34), for treatment of hypoparathyroidism, and osteoporosis.

Entera's proprietary platform technology consists of two components: a small molecule that enhances the absorption of a large molecule therapeutic agents and a second component that "protects" the large molecule from digestion in the gastrointestinal tract. This synergistic system is intended to increase oral bioavailability and decrease the variability associated with the oral administration of large molecule biologics and synthetic protein therapeutic agents.

Currently, biological entities and other large molecules can only be delivered via injections and or other non-oral pathways. However, oral drug delivery is the easiest method for self-administering medications, offers patients greater dosing flexibility, and has the highest patient acceptance and compliance rates as compared to all other routes of drug administration. For more information, visit www.enterabio.com.

Merus Announces Strategic Collaboration With Betta Pharmaceuticals

Merus N.V. recently announced it has agreed to grant Betta Pharmaceuticals Co Ltd an exclusive license to develop and commercialize Merus Biclonics MCLA-129 in China. Merus will retain all rights outside of China.

Under the terms of the agreement, Betta Pharmaceuticals has agreed to be responsible for clinical development and commercialization of MCLA-129 in China. As a key strategic component of the collaboration, Betta will retain a contract manufacturing organization with experience in filing Initial New Drug (IND) applications with US and European regulatory authorities in order to produce clinical trial materials for the Chinese market and rest of world. Betta will facilitate regulatory filings and early stage clinical trial materials supply for potential use by Merus for development of MCLA-129 outside of China.

"This latest collaboration is representative of our long-term strategy to unlock Biclonics platform value beyond our core programs," said Ton Logtenberg, PhD, Chief Executive Officer of Merus. "Betta Pharma is a market leader in EGFR inhibitors in China and we anticipate will be a strong partner for Merus in MCLA-129 development."

MCLA-129 is a Biclonics binding to EGFR and cMET for the treatment of solid tumors. EGFR is an important oncogenic driver in many cancers; the upregulation of c-MET signaling has been associated with resistance to EGFR inhibition.

MCLA-129 has two distinct mechanisms of action. First, Merus' Dock & Block mechanism of action blocks the signaling of EGFR as well as c-MET, with the potential to inhibit tumor growth and survival. Second, MCLA-129 utilizes GlymaxX antibody-dependent cell-mediated cytotoxicity (ADCC)-enhancement technology designed for greater cell-killing potential. Because the Dock & Block and ADCC mechanism of action is based on the co-expression of EGFR and c-MET, it is expected to have less toxicity compared to agents targeting EGFR alone.

In preclinical studies, MCLA-129 showed a significant reduction in tumor volume for EGFR inhibitor-resistant lung cancer models lacking immune cells. Additionally, in cell lines that co-express both EGFR and c-MET, MCLA-129 effectively induced tumor cell lysis at low antibody concentrations.

In addition to receiving an upfront payment, Merus will be eligible to receive payments contingent upon Betta Pharmaceuticals achieving certain specified development and commercial goals in China. Merus will also be eligible to receive tiered royalty payments on sales in China from Betta Pharmaceuticals. Betta Pharmaceuticals will be eligible to receive payments contingent upon Merus achieving certain specified development and commercial goals, and will be eligible to receive tiered royalty payments on sales outside of China from Merus.

Merus is a clinical-stage immuno-oncology company developing innovative full-length human bispecific antibody therapeutics, referred to as 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.

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Acer Therapeutics Announces Exclusive License Agreement With Sanofi

Acer Therapeutics Inc. recently announced it has entered into an exclusive license agreement with Sanofi to acquire worldwide rights to osanetant, a clinical-stage, selective, non-peptide tachykinin NK3 receptor antagonist. Acer plans to initially pursue development of osanetant as a potential treatment for certain neuroendocrine-related disorders. Financial terms of the license agreement were not disclosed.

"We are thrilled to expand our pipeline of product candidates by in-licensing the global rights to osanetant," said Chris Schelling, CEO and Founder of Acer. "The drug perfectly fits Acer's acquisition and development model of de-risked assets – it already has robust non-clinical, pharmacokinetic and human safety data, and based on recent studies involving antagonism of the NK3 receptor, we believe it can be successfully repurposed to treat a variety of neuroendocrine disorders. We very much appreciate the opportunity to expand our relationship with Sanofi."

"We are pleased to sign this agreement with Acer, which illustrates our strategy of collaborating with partners who bring a credible repurposing strategy to non-core molecules in our broad portfolio," said Alban De-La-Sabliere, Global Head of Business Development and Licensing at Sanofi. "By providing access to these select R&D programs, we can continue to support efforts to address serious unmet medical need."

Acer, headquartered in Newton, MA, is a pharmaceutical company focused on the acquisition, development, and commercialization of therapies for serious rare and life-threatening diseases with critical unmet medical need. Acer's pipeline now includes three clinical-stage candidates: EDSIVO (celiprolol) for the treatment of vascular Ehlers-Danlos Syndrome (vEDS) in patients with a confirmed type III collagen (COL3A1) mutation; ACER-001 (a fully taste-masked, immediate-release formulation of sodium phenylbutyrate) for the treatment of various inborn errors of metabolism, including urea cycle disorders (UCD) and Maple Syrup Urine Disease (MSUD), and osanetant for the treatment of various neuroendocrine disorders. Acer's product candidates are de-risked, having one or more of a favorable safety profile, clinical proof-of-concept data, mechanistic differentiation, and an accelerated path for development, which may include utilizing expedited programs (eg, Priority Review) established by the FDA and/or using the regulatory pathway established under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FFDCA) that allows an applicant to rely at least in part on third-party data for approval, which may expedite the preparation, submission, and approval of a marketing application. For more information, visit www.acertx.com.

Sarepta Therapeutics Enters Strategic Relationship With Aldevron

Sarepta Therapeutics, Inc. and Aldevron recently announced they have entered into a long-term strategic relationship for the supply of plasmid DNA to fulfill Sarepta's needs for its gene therapy clinical trials and commercial supply. Under the terms of the agreement, Aldevron will provide GMP-grade plasmid for Sarepta's micro-dystrophin Duchenne muscular dystrophy (DMD) gene therapy program and Limb-girdle muscular dystrophy (LGMD) programs, as well as plasmid source material for future gene therapy programs, such as Charcot-Marie-Tooth, MPS IIIA, Pompe and other CNS diseases.

"One of our highest priorities is building a robust supply chain and scalable manufacturing that can accelerate and ensure robust patient access to our pipeline of promising gene therapies on an accelerated timeline," said Doug Ingram, Sarepta's President and Chief Executive Officer. "Aldevron, one of the top plasmid DNA manufacturers in the world, is an important partner in fulfilling our strategic objectives. This agreement is anticipated to provide sufficient plasmid supply to support our ambitious development and commercial gene therapy objectives."

"Our greatest satisfaction comes in helping companies whose research is making an impact on the lives of patients, and we are proud to partner with Sarepta, a company dedicated to extending and saving lives," said Michael Chambers, Chief Executive Officer and Co-founder of Aldevron. "Aldevron has made significant investments in people, processes, and facilities to support the pre-clinical, clinical, and commercial production of new, genetically based therapies that have significant potential in transforming disease."

Sarepta is at the forefront of precision genetic medicine, having built an impressive and competitive position in Duchenne muscular dystrophy (DMD) and more recently in gene therapies for 5 Limb-girdle muscular dystrophy diseases (LGMD), Charcot-Marie-Tooth (CMT), MPS IIIA, Pompe and other CNS-related disorders, totaling over 20 therapies in various stages of development. The company's programs and research focus span several therapeutic modalities, including RNA, gene therapy, and gene editing. Sarepta is fueled by an audacious but important mission: to profoundly improve and extend the lives of patients with rare genetic-based diseases. For more information, visit www.sarepta.com.

Founded in 1998, Aldevron supplies plasmid DNA and gene editing enzymes to biopharmaceutical researchers developing advanced gene-based medicines. Aldevron also provides recombinant biological products for veterinary and agriculture applications. Aldevron specializes in GMP manufacturing and is known for inventing the GMP-Source™ quality system. Company headquarters are in Fargo, N.D., with additional facilities in Madison, WI., and Freiburg, Germany. For more information, visit www.aldevron.com.

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Formulation Forum

Sophisticated Formulation Approaches for Insoluble Drug Candidates

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

"Fools ignore complexity. Pragmatists suffer it. Some can avoid it. Geniuses remove it" — Alan J. Perlis

Jim Huang, PhD
Founder & CEO
Ascendia Pharmaceuticals

On many occasions, people have approached me with questions, such as "Are solution formulations a good, simple approach, whereas are nano-formulations too complex?" Or "What is a sophisticated formulation, and what role do nano-formulations play to accelerate the drug discovery/development process to the clinic?"

Undoubtably, there is no straight answer to those questions. As an example, for poorly water-soluble compounds with chemical instability, the development of a stable solution formulation with reasonable drug loading is a daunting task. By utilizing a nano-formulation approach, this formulation strategy may resolve the drug-loading and bioavailability issues for such compounds, while adding minimum complexity to the manufacturing process.

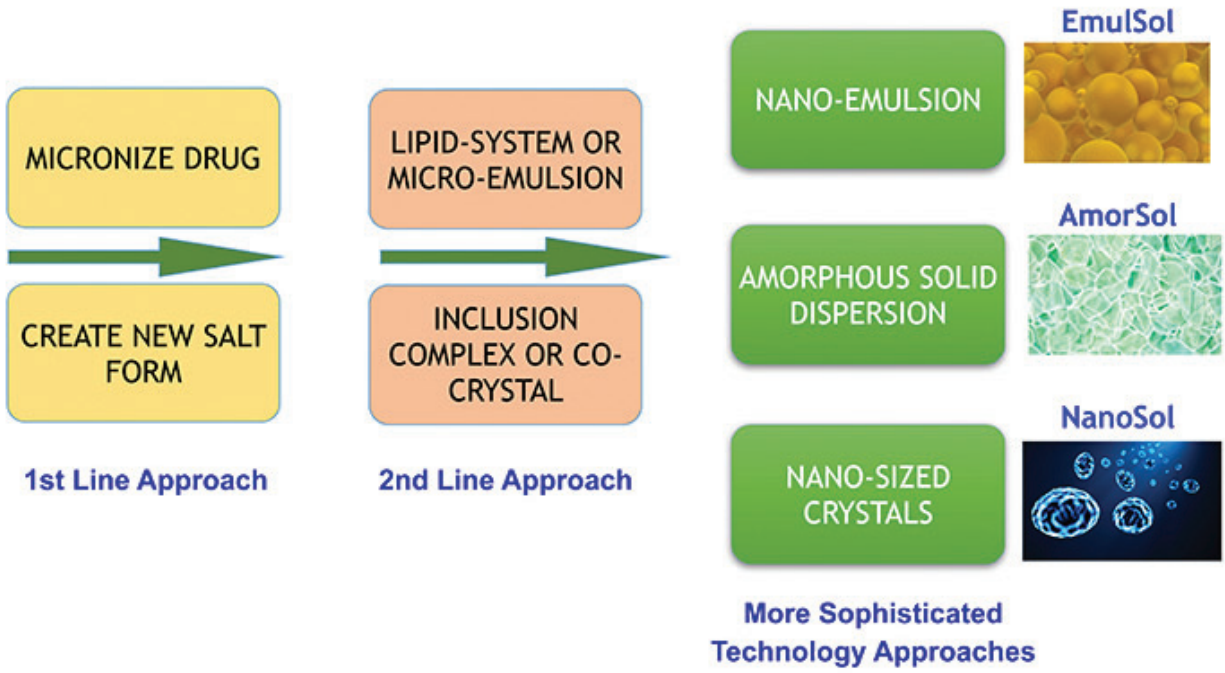
We all realize drug discovery and development is a very complex process requiring a stepwise and systematic approach to select compounds that have desirable therapeutic properties and are suitable for advancement into drug candidates and final drug products. A sophisticated drug delivery approach involves collaboration, technical experience, and years of working knowledge in drug development at different stages of the process. Our approach to drug development involves a thorough understanding of the physical-chemical and biopharmaceutical properties in relation to drug dissolution, absorption, and the disposition process in the body, while taking advantage of our nano-based formulation technology success. The goal being to ensure successful development of a fit-for-purpose, phase-appropriate formulation that is right the first time in an accelerated and quality manner.

There are many significant hurdles for a pharma or biotech company to overcome during the development process. The high failure rate in drug development shows that only 1 in 5,000 discovery compounds will reach the market, and 1 in every 5 drug candidates will gain approval.[1] The average time from drug discovery to product launch is estimated to be ~14 years. As a result, the overall costs of drug discovery and development to bring a new medicine to the market are estimated at over $1 billion for a new chemical entity (NCE).[2]

Most failures in early development are mainly due to drug toxicity or safety issues, whereas a lack of efficacy is the primary reason for late-stage failure.[3] The lengthy development time has been attributed to an increase in the preclinical phase to select the candidate drug. Our focus is to provide formulation and cost advantages to reduce this time in the preclinical phase. A significant increase in the percentage of NCEs with poor physical, chemical, and biopharmaceutical properties (BCS II and IV) in the drug pipeline has played a significant role in attributing to those high failure rate and increase in development timelines.[4] About 50% of drugs on the market and nearly 90% of molecules in the discovery pipeline are poorly water soluble.[5] Poor solubility can lead to low bioavailability, resulting in suboptimal drug delivery, ineffective drug efficacy, and side effects. As a result, various drug delivery nano-technologies, such as nano-suspensions, lipid microemulsions, nano-emulsions, and amorphous solid dispersions, can play an important role to overcome these bioavailability challenges faced by pharma and the biotech industry.

Using some of these drug development platforms, we have seen effective formulations with good bioavailability enable better assessment of the pharmacology, toxicology, safety, and efficacy properties of a compound during drug discovery and

FIGURE 1



development. The results of these successful formulations can be seen in the positive pharmacokinetics, pharmacodynamics, and toxicological profiles of the drug candidate assessed in association to the biological response to specific drug targets.

Each drug discovery and development stage has its own limitations and requirements in terms of route of administration, doses, and impact of vehicle components. The objectives and specific designs of the formulation approach can vary significantly depending on the development stage. Broadly speaking, these can be classified into seven categories: 1) validation of a new target with a new pharmacology model; 2) DMPK and pharmacology for lead optimization; 3) biopharmaceutical evaluation for lead identification; 4) pre toxicological reading; 5) IND-enabling tox studies, 6) early phase (Phase 1/2a) developments; and 7) late-stage commercial development (Phase 2b & Phase 3).

Depending on a compound's physical, chemical, and biopharmaceutical properties, a rational formulation design can be explored with guidance from a decision tree. Numerous drugs associated with poor solubility and low bioavailability have been successfully formulated into drug products for clinical studies by a suite of available formulation technologies (Figure 1). Many marketed drugs have been successfully reformulated to improve efficacy, safety, and patient compliance using the NDA 505(b)(2) regulatory pathway. Revitalization of older marketed drug products using innovative drug delivery technologies or platforms can provide new marketing exclusivity and new patent protection, and thus offer an effective tool for product life cycle management.

Future Formulation Forums will cover a series of topics in various stages of formulation development from discovery support and candidate drug selection to development of clinical dosage forms with an emphasis on the application of chemistry, preformulation, biopharmaceutics, and novel formulation principles. ◆

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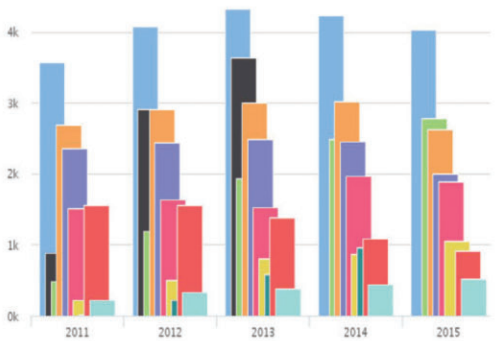

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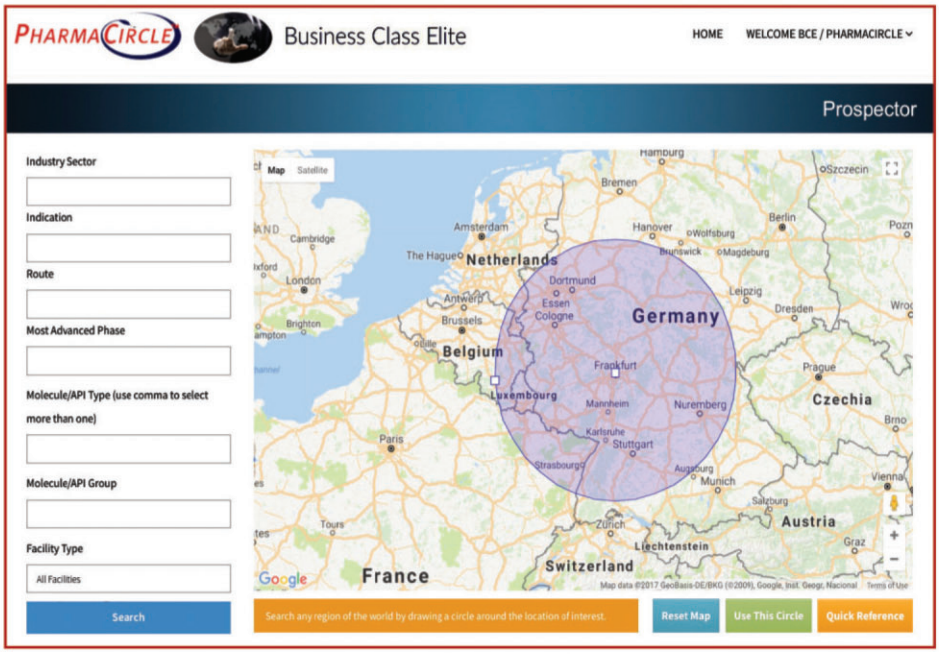

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EXTRACTABLES & LEACHABLES

A Practical Approach to Extractables & Leachables

By: Cheryl Johnson

INTRODUCTION

The study of extractables and leachables (E&L) has been evolving for many years. As pharmaceutical manufacturers, packaging vendors, and regulatory agencies gain more knowledge of extractable compounds, the scope of E&L guidelines grows with it. Many of the case studies that initiated interest in extractables and leachables are based on primary packaging. In some cases, the secondary or tertiary packaging were identified as sources of leachables. As a result, the primary emphasis of extractables screens has been on the packaging systems. The approach to these screens is well established. The first iterations of regulatory guidance addressed the common packaging materials in the United States Pharmacopeia (USP) chapter <661>, which relied heavily on physiochemical testing to characterize the material of construction but did not directly address extractables testing of the final packaging materials in detail. With advancements in the manufacture of plastics and increasing variety of base polymers used for packaging systems, it became evident that more specific guidelines are needed.

In an effort to provide clarity with respect to extractables and leachables used in primary packaging and the manufacture of drug products, USP introduced a series of chapters specifying the approach to characterize and qualify both packaging and manufacturing systems with respect to patient safety. USP chapter <661> was split in two: chapter <661.1> *Plastic Materials of Construction*, which deals with identification, physiochemical properties, and bioreactivity of the materials of construction only, and <661.2> *Plastic Packaging Systems for Pharmaceutical Use*, which addresses the final packaging system and establishes its suitability for intended use. Additionally, as the components used in manufacturing become of increasing interest as sources of potential leachables, the industry must prepare for the new guidelines. Furthermore, the rising popularity of biologics and the relative complexity of their manufacture warrants a comprehensive framework for determining the risk of drug-product-material interaction. A systematic approach to addressing these materials more specifically is introduced in draft USP chapters <665> *Polymeric Components and Systems Used in the Manufacture of Pharmaceutical and Biopharmaceutical Drug Product* and <1665> *Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products*. While the latter two chapters are not yet official, the purpose of these chapters is to explicitly include requirements for extractables and leachables, it is prudent to get acquainted with the content.

The final chapter, which became effective in conjunction with <1663> *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* is <1664> *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems*. The purpose of this chapter is to outline the basis of a leachables assessment of packaged drug product, the determination of an appropriate analytical evaluation threshold, and to establish an extractables-leachables correlation. Guidelines for the long-term strategy for monitoring target compounds, such as method validation, development of specification, etc. are also listed in this chapter.

Despite developing regulation, it is not possible to list the best approach for each drug product packaging or manufacturing configuration in these chapters, as each of these chapters refers the reader to the extractables foundation chapter <1663> for the for the design, justification, and execution of an extractables assessment.[1]

"The completeness of an extractables and leachables assessment hinges on the goals of the study. If scientifically sound principles are used to justify the study design, parameters appropriate for the drug product surface interaction, and a sufficiently conservative AET are selected, then an applicant can confidently conclude whether their packaging system is suitable for its intended use and free from process equipment-related leachables."

THE EXTRACTABLES SCREEN

USP chapter <1663> *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* is the basis for the chemical safety assessment section of USP <661.2>, the organic extractables profile of draft USP <665>, and the chemical safety qualification of draft USP <1665>. It is, therefore, the cornerstone to determine whether a packaging system is suitable for its intended use and free from process equipment-related leachables at levels of toxicological concern. A primary packaging extractables screen classically includes exposing the primary packaging to conditions far greater than it will ever encounter, in order to build a worst-case profile. The key characteristics of a scientifically rigorous extractables study generally include driving analytes into solution in the laboratory for subsequent analysis via a variety of complementary techniques. The critical parameters for any extraction study are:

- A range of solvents for purposes of targeting a variety of potential leachables
- Conditions appropriate for the drug product/packaging system configuration
- Generation of extracts that contain potential leachables at levels that exceed the sensitivity of the analytical methods
- Complementary analytical methods that combine to develop a worst-case leachables profile

Extract generation should occur in a medium that mimics the formulation and brackets the pH range of the final product to target organic extractables. A third solvent to target organic extractables is an aggressive solvent designed to generate the maximum concentration of potential leachables without compromising the integrity of the container. In addition, a solvent designed to drive any inorganic leachables into solution should be used. By employing a range of solvents, the solutions are more likely to include leachable compounds with diverse properties; however, the extraction conditions are also important.

Solvent selection establishes the appropriate media into which the extractables will be observed, but time and temperature are what will drive the extraction. Since the goal of the study is to simulate the duration of shelf-life in a condensed period of time, the use of Arrhenius scaling is recommended to determine the appropriate level of aging in the laboratory.[1] Exposing the packaging system to extreme conditions is best applied to componentry that will be in direct contact with the formulation for the duration of the drug product shelf-life. However, due to short exposure time and relatively mild conditions that a component used for manufacturing is in contact with the formulation an extractables screen of these materials can employ much milder conditions and fewer solvents.

SIMULATING EXTRACTABLES IN MANUFACTURING SURFACES

Many components used in the manufacture of drug products are polymeric single-use systems (SUS). Single-use systems are gaining popularity for a variety of reasons: mitigating costly cleaning validations, minimizing "down-time" in between batches, and as is often the case for biopharmaceutical manufacturing, may be the only substrate suitable for manufacture. Consequently, the expansive options of SUS on the market must also be deemed suitable for their intended use, but the means to that determination does not require the extreme conditions typically used

for packaging systems. Traditional extraction techniques may be used, but they carry the risk of degrading the test article, which results in lengthy justification for extractable compounds that will not be observed as leachables. The transient exposure of a drug product formulation to the manufacturing component justifies a "softer" approach to the extractables screen. By simulating slightly exaggerated manufacturing conditions in the lab, the study can account for potential extractables in line with the probability that they will be observed in real-time and mitigate the aforementioned risks.

Simulation studies can be limited to two solvents and exposure conditions chosen to extend slightly beyond manufacturing conditions, as a complete profile can be obtained with this simplified approach. For example, using placebo or drug product as an extraction solvent will serve as a representative of the manufacturing process. An aggressive solvent can be used as a second extraction solvent to aid qualitative evaluation of the formulation sample and represent a positive control. Using an aggressive solvent has the additional benefit of showing the analytical methods are capable of detecting the target compounds.

CHARACTERIZING THE EXTRACTS

It is important to perform the extraction at a scale that will yield concentrations of leachables at levels that will be analytically significant in order to characterize the extracts. This may be accomplished at the time of preparation or via manipulation of the test solution after extraction.

Extract characterization is best performed using complementary analytical techniques. Mass spectrometry coupled with chromatographic systems (such as gas or liquid) are powerful investigative tools that will provide structural information needed to categorize and/or identify organic extractable compounds. Gas chromatography-mass spectrometry (GC/MS) analytical methods must be designed to detect organic compounds across a range of boiling points to capture semi-volatile and volatile extractables. Liquid chromatography-mass spectrometry (LC/MS) methods, though limited in peak identification capabilities, can provide valuable structural information of non-volatile extractables. In many cases, the identity of a compound can be ascertained through the use of commercially available libraries, internal databases, and in-house expertise. In the case where a compound cannot be readily identified, structural analysis may be performed in order to glean any potentially useful information. Analysis for inorganic compounds, commonly referred to as "extractable metals," can be evaluated using Inductively-Coupled Plasma Mass Spectrometry (ICP/MS). ICP/MS is the most common platform for assessing elemental impurities, and the same techniques can be used to determine elemental leachables.

DETERMINATION OF THE ANALYTICAL EVALUATION THRESHOLD

Pairing the appropriate extraction conditions with a conservative Analytical Evaluation Threshold (AET) results in a well-rounded profile of potential leachables in packaging systems or manufacturing equipment. The AET for extraction studies is one of the most critical elements of the study design because it represents the threshold for which the applicant commits to further investigation if a compound is observed. It is the threshold for which the packaging system or manufacturing equipment may be deemed safe for its intended use. Therefore, it is imperative to design the study such that the resulting solutions contain concentrations of compounds of interest, if present, above this threshold in order for the data to support this conclusion.

The AET is the link between a Safety Concern Threshold (SCT) published by various agencies that determine acceptable daily intake of potentially toxic compounds and the specific drug product. The SCT for genotoxic compounds which is 1.5 µg/day per USP, Product Quality Research Institute (PQRI), and International Conference on Harmonisation (ICH) guidelines is the most common basis for the AET as it is the most conservative for oral and parenteral drug products.[2-9] To calculate the AET the maximum daily dose of the drug product and the SCT are combined with a 50% uncertainty factor to accommodate variations in response of the target compounds. The final AET is a drug product specific value typically expressed in units per component or units per day. For example, AET calculation (µg/vial) for primary packaging, daily dose one vial per day:

$$\frac{1.5\ \mu g}{day} * 50\%\ Uncertainty\ Factor * \frac{1\ day}{1\ vial} = 0.75\ \mu g/vial$$

When scaling this calculation for manufacturing surfaces, the AET will often be milligram-level per batch because the batch size is typically tens or hundreds of liters, or thousands of vials. Consider the aforementioned example, applied to a manufacturing scale batch size, AET calcu-

lation (µg/component) for manufacturing surfaces, 20L batch size for a 1.5 mL fill:

$$\frac{1.5\,\mu g}{day} * 50\%\,Uncertainty\,Factor * \frac{1\,day}{1\,vial} * \frac{1\,vial}{1.5\,mL} * \frac{20000mL}{Batch} * \frac{1Batch}{1Component} * \frac{1\,mg}{1000\,\mu g} = 10\,mg/component$$

Due to the size and complexity of many components of typical manufacturing processes, none of which is anticipated to exceed one kilogram in total weight, a more conservative approach is a materials-based AET of 1 µg/g of material. If a component does weigh one kilogram, this AET represents a ten-fold more conservative AET, as shown in the following calculation:

$$\frac{1\,\mu g}{1\,g} * \frac{1000\,g}{1\,Component} = 1\,mg/component$$

The extraction screen is intended to represent a worst-case scenario of potential leachables. The studies are designed to mimic shelf-life under extreme conditions. The leachables assessment is the final step in the evaluation process. The core concepts of analysis and AET previously discussed are applied to aged drug product. Drug product, aged under accelerated conditions, is analyzed for the same range of compounds. In this context, however, if these compounds are observed, they can be considered bona fide leachables rather than potential leachables. Moving forward, the applicant will have to consider next steps by referring to a toxicologist for recommendations on specific compounds, validating methods for monitoring target compounds on stability, or in the event no leachables are observed, justifying completion of the leachables assessment.

The completeness of an extractables and leachables assessment hinges on the goals of the study. If scientifically sound principles are used to justify the study design, parameters appropriate for the drug product surface interaction, and a sufficiently conservative AET are selected, then an applicant can confidently conclude whether their packaging system is suitable for its intended use and free from process equipment-related leachables. A leachables assessment of aged drug product will support the justification of compliance or direct the continued monitoring over time, if compounds are observed.

The implications of upcoming regulatory guidelines have the potential to compromise the timelines of pharmaceutical and biopharmaceutical applicants as vendors implement internal strategies to align with evolving regulation. After significant industry feedback, applicants were permitted to defer to the original <661>, but the implementation window for chapters <661.1> and <661.2> closes in early 2020. The draft chapters <665> and <1665> are in the pipeline. Therefore, it is imperative to understand the underlying principles of foundation chapter <1663> and apply the concepts therein to prepare a complete assessment of potential leachables in drug product manufacturing or packaging systems. ◆

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BIOGRAPHY

Cheryl Johnson is the Commercial Development Manager of Biotechnology at Alcami. She has more than 15 years of industry experience in research and manufacturing scale laboratories, and her areas of expertise include analytical and preparative chromatography, mass spectrometry, method development, and validation with specialized knowledge of regulatory compliance relating to extractables and leachables. She joined Alcami in 2014 as a scientist and is a technical lead for Alcami's Biotechnology and Structural Chemistry-related offerings.

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TRANSLATIONAL PHARMACEUTICS

Accelerating Early-Stage Drug Development With Integrated CDMO & CRO Services

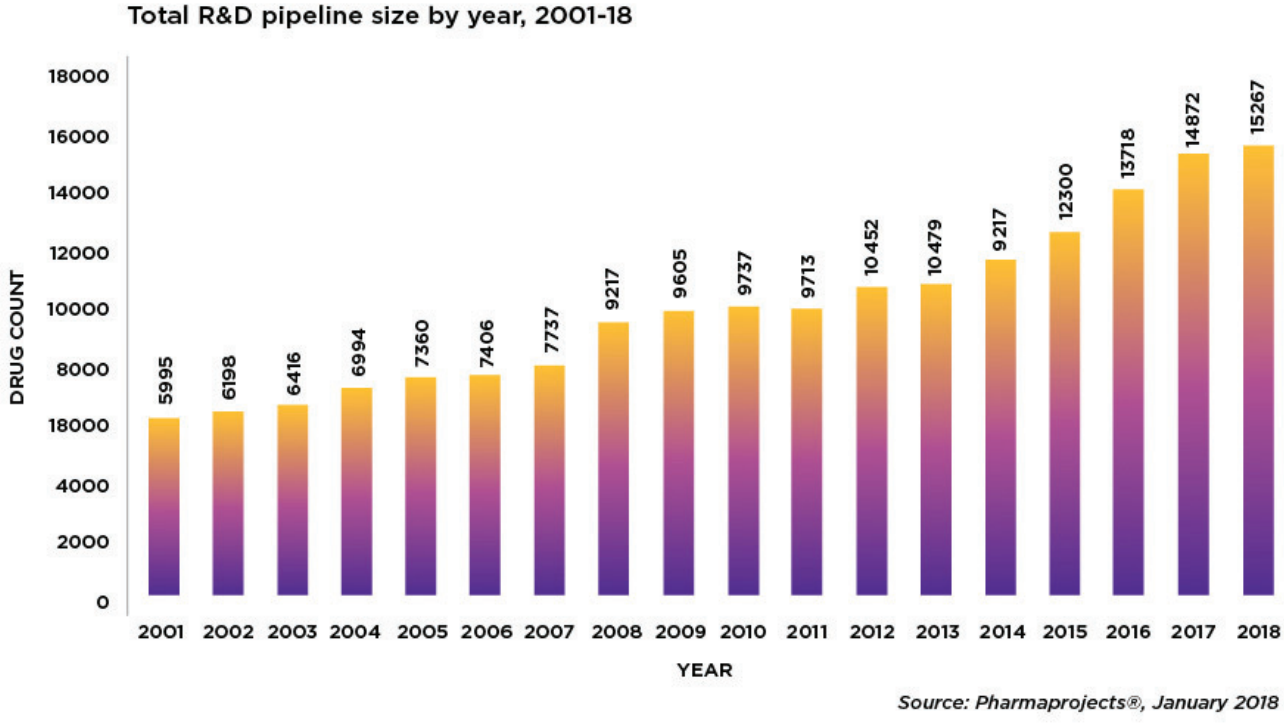
By: Peter Scholes, PhD

THE R&D CHALLENGE

Throughout the past two decades, the pharmaceutical research and development (R&D) ecosystem has grown exponentially. Between 2001 and 2018, the number of therapeutic molecules under development has more than doubled (Figure 1), and the number of companies actively engaged in research has more than tripled.[1] However, R&D failures remain high, and approximately 90% to 95% of drugs fail before reaching the marketplace, according to most industry estimates.

To conserve resources and get drugs to market faster, drug developers around the world are seeking new ways to make development more cost-effective and efficient. Across the industry, from virtual biotech to large pharma, drug companies are increas-

FIGURE 1



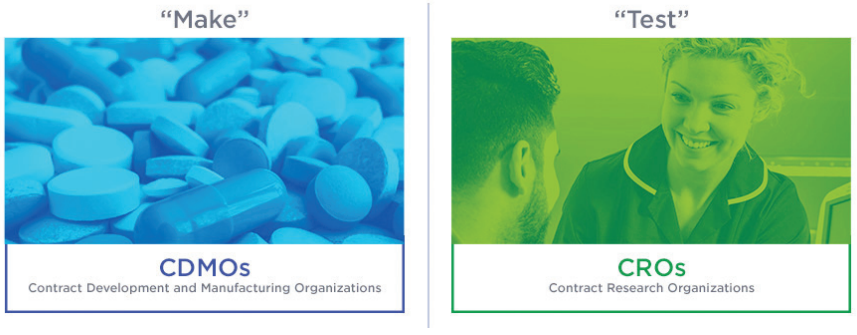
ingly relying on outsourcing partners to access capacity and new technologies in an attempt to address these challenges and develop a competitive edge.

Those efforts have generated an explosion of outsourcing initiatives throughout the past 10 years that have driven a fundamental change in how the industry is structured. Components of the drug development process are being handed over to contract development and manufacturing organizations (CDMOs) and contract research organizations (CROs) — from project-based outsourcing, to full-time equivalent and contract labor models and, in some cases, to full development programs.

The result, however, has arguably been the emergence of a plethora of disparate and non-integrated CDMOs and CROs, reflecting the structures and inefficiencies that previously existed within pharma organizations. Each provider handles its own discrete functional activities — from discovery chemistry, preclinical toxicology, clinical research, formulation development and manufacturing — and this has created separate and siloed CDMO ("make") and CRO ("test") supply chains (Figure 2). This multi-vendor environment hampers efforts to streamline the drug development process and has drug companies struggling to manage programs effectively and maintain productivity.

This article describes the current challenges and questions (see bullet points) faced by drug developers in accelerating molecules to proof-of-concept (POC) and developing optimized and scalable drug products for patient trials. It summarizes the benefits an integrated CDMO/CRO outsourcing model brings to managing resources and improving the drug development process. This approach, which has been proven to be successful in Europe, is now being operationalized in the United States.

FIGURE 2



CHALLENGES & QUESTIONS FACED BY DRUG DEVELOPMENT TEAMS

- How can I quickly start a first-in-human (FIH) clinical trial?
- How can I develop and manufacture fit-for-purpose early-phase clinical materials?
- How can I progress into the clinic with limited quantities of drug substance?
- How can I rapidly evaluate formulation options before starting a pivotal trial?
- How can I overcome formulation challenges such as low solubility?
- How do I switch from a simple formulation to a patient-suitable drug product without losing time?
- How can I manufacture drug product on demand to meet the precise needs of the clinical trial and patient recruitment?
- How can I manage the amount of drug substance and drug product required for clinical development?

IMPROVED R&D REQUIRES INTEGRATION

To keep pace, drug developers require new strategies to help them achieve milestones as quickly as possible. As a consequence, we are seeing innovation in the service sector, with a focus on smarter R&D in which multiple CDMO and CRO services and activities are becoming highly integrated within a single vendor, under a compressed timeline. This strategy, which has been used successfully in Europe for more than a decade, allows the outsourcing partner to coordinate and adapt the drug product manufacturing requirements ("make") with the specific needs of the clinical development plan ("test").

Quotient Sciences has pioneered an integrated approach that streamlines development processes and fosters a consistent exchange of information (Figure 3). The operational footprint and framework to run these integrated "make-test" programs under an investigational new drug (IND) application has recently been established in the United States. This opens up advantages to biotechnology and pharmaceutical companies in the world's largest R&D market, where the greatest number of molecules are in development.

FIGURE 3

With an integrated approach, multiple CDMO ("make") and CRO ("test") activities are performed using a single vendor, under a compressed timeline.

REAL-TIME ADAPTIVE MANUFACTURING: INTEGRATED WITH CLINICAL TESTING

The early stages of clinical development are particularly amenable to implementing an integrated platform. The horizontal integration of CDMO and CRO capabilities enables a shortened make-test cycle where a trial sponsor can integrate drug product manufacturing within the clinical program.

Shortened Cycle Times

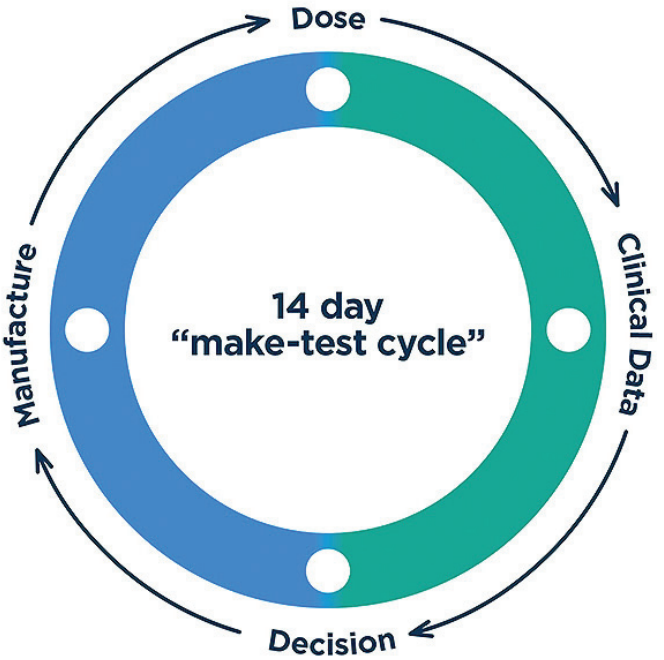
Using a fit-for-phase manufacturing strategy, make-test cycles can be as short as days rather than weeks or months. In a 14-day cycle time, for example, products are manufactured in real time at the precise dose or composition required, immediately before dosing the volunteers or patients in a clinical trial. The drug product can then be fine-tuned in response to the clinical safety, pharmacokinetic (PK) and pharmacodynamic (PD) data emerging from within the study. This process reduces chemistry, manufacturing and controls (CMC) investments, conserves drug substance and allows human data to drive key decisions (Figure 4).

Formulation Design Space Flexibility

It is difficult to predict the quantitative levels of critical-to-performance components in a drug formulation that enables the program to achieve the desired clinical endpoints. Traditionally, development teams rely on surrogate, non-clinical, *in vitro* or *in silico* tools to determine that information before beginning a study, but that means accepting a certain level of risk. In an integrated approach, inclusion of a formulation design space enables real-time flexibility to adjust the quantitative composition of the formulation based on emerging clinical data (Figure 5).

Coupled with real-time manufacturing, it is possible to assess multiple formulation technologies and drug products in a clinical trial without having to secure regulatory or institutional review board (IRB) approval every time the dose or formulation is adjusted. The drug company efficiently manufactures optimized drug products and moves through early development, adapting quickly to any emerging PK, PD or safety data (in FIH and dose escalation trials).

FIGURE 4



"Quotient Sciences has pioneered an integrated approach that streamlines development processes and fosters a consistent exchange of information. The operational footprint and framework to run these integrated 'make-test' programs under an investigational new drug (IND) application has recently been established in the United States. This opens up advantages to biotechnology and pharmaceutical companies in the world's largest R&D market, where the greatest number of molecules are in development."

KEY APPLICATIONS OF AN INTEGRATED CDMO/CRO MODEL

Specifically, this type of integrated program allows drug companies to:

Accelerate Molecules From First-in-Human to Proof-of-Concept

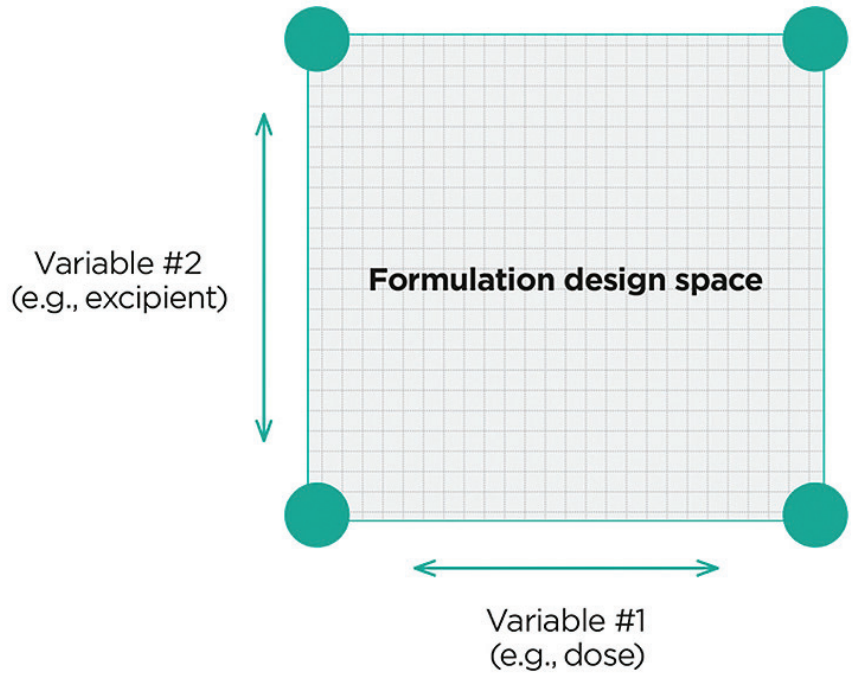
For an FIH study, a simple fit-for-phase drug product strategy is typically used to provide dose flexibility with minimal upfront investments. However, this does not address the risks of poor oral bioavailability due to challenging drug chemistry, or the need to identify a solid oral dosage form for POC. Through the use of real-time adaptive manufacturing, it is possible to alter dose levels, formulations and drug product types within the clinical trial, without amending the protocol, and then maintain a seamless supply of the lead drug product as the drug candidate progresses into downstream patient trials.

Benefit From Real-Time Adaptive Manufacturing for Patient Trials

Real-time adaptive manufacturing offers a creative but simple solution in early patient trials. Biotech and pharma companies can balance the clinical requirements (e.g., patient recruitment) with the CMC requirements (e.g., shelf-life and drug product availability), ultimately manufacturing only the precise drug product required to meet the needs of the clinical trial.

This approach conserves valuable drug substance and reduces drug product manufacturing costs until such time that scale-up is required to support late-phase trials and commercialization. Real-time manufacturing can even occur on a per-patient basis, which is especially beneficial with orphan drugs, rare diseases and pediatric indications in which patients are often enrolled one at a time and the prod-

FIGURE 5



Formulation design spaces enhance the flexibility of a clinical trial protocol by allowing a trial sponsor multiple degrees of freedom to test various formulations and drug products during a study. For example, when developing a modified-release matrix tablet formulation, it is possible to vary the drug content and release-controlling polymer content in a two-dimensional space to optimize both the shape of the PK profile and its position within the therapeutic window. For more complex formulations, flexibility to adjust three, four or even five variables can be embedded within the program.

uct may need to be "tuned" to specific subject needs.

Develop Optimized & Scalable Drug Products

Most new drugs emerging from the industry pipeline have sub-optimal properties and require formulation optimization to achieve their full potential, either after POC or as part of life-cycle management. Real-time adaptive manufacturing can be integrated into clinical bioavailability and PK studies to screen, optimize and select new formulations based on emerging clinical data. Using this approach, multiple formulation technologies can be evaluated head-to-head and design space flexibility exploited to optimize the quantitative composition and dosage strengths relative to clinical performance.

THE BENEFITS OF AN INTEGRATED APPROACH

Aligning the "make" and "test" cycles of the research process fosters a consistent exchange of information and allows the outsourcing partner to adapt and fine-tune both the formulation composition and manufacturing process to the specific needs of the clinical trial.

With compounded timeline savings of more than six months, investment savings of more than $500,000 and drug substance conservation of up to 85%, an integrated early development program not only improves trial efficiency, it significantly improves productivity and eases the drug company's management burden. An integrated approach improves development precision, maximizing a drug candidate's potential for success within a single study and ultimately delivering new medicines to the people who need them faster.

SUMMARY: IMPLEMENTING AN INTEGRATED APPROACH

Integrated approaches have been used successfully in Europe since 2007. The Medicines and Healthcare products Regulatory Agency (MHRA) recognized the advantages of combining real-time adaptive manufacturing and flexible clinical protocols in early development, and these principles are now widely accepted in the United Kingdom. Throughout the past decade, more than 350 integrated Translational Pharmaceutics® programs have been conducted for biotech and pharmaceutical companies from the United States and around the world.

Because the operational framework to run integrated programs under an IND application has recently been established, the same benefits can now be realized in the United States. By adapting an approach such as the aforementioned make-test cycle, drug developers can shorten the typical drug development timeline by six months or more, which — for a drug product forecasted to generate $500 million to $1 billion in annual revenue — can enable developers to conserve millions of dollars per day. And, when drugs get to market faster, we all benefit. ◆

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BIOGRAPHY

Peter Scholes, PhD, is the Chief Scientific Officer of Quotient Sciences. With over 20 years' experience in the pharmaceutical industry, he joined Quotient Clinical in 2007, where he has developed and built the pharmaceutical sciences group. He was instrumental in identifying and implementing the innovative and flexible benefits of integrating pharmaceutical development and clinical testing in early research. Since being named Quotient's CSO in 2013, he has been responsible for the scientific strategy and leadership for the organization.

Earlier in his career, Dr. Scholes held various roles at 3M Pharmaceuticals and 3M Drug Delivery Systems. He has served as a committee member for the U.K. Controlled Release Society and APS Biopharmaceutics Focus Group, and, in 2013, he set up a GastroPlus user group with industry colleagues as a discussion forum for PBPK modeling and simulation science. Named in 2010 as one of PharmaVOICE's 100 most inspiring people in the life sciences industry, Dr. Scholes holds a doctorate degree in pharmaceutical sciences from the University of Nottingham and was appointed as an honorary professor at that university in 2015.

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CLINICAL ANALYTICS SOLUTIONS

Reducing Clinical Cost Budget Variations With State-of-the-Art Data Lifecycle Management Solutions

By: Srini Anandakumar

INTRODUCTION

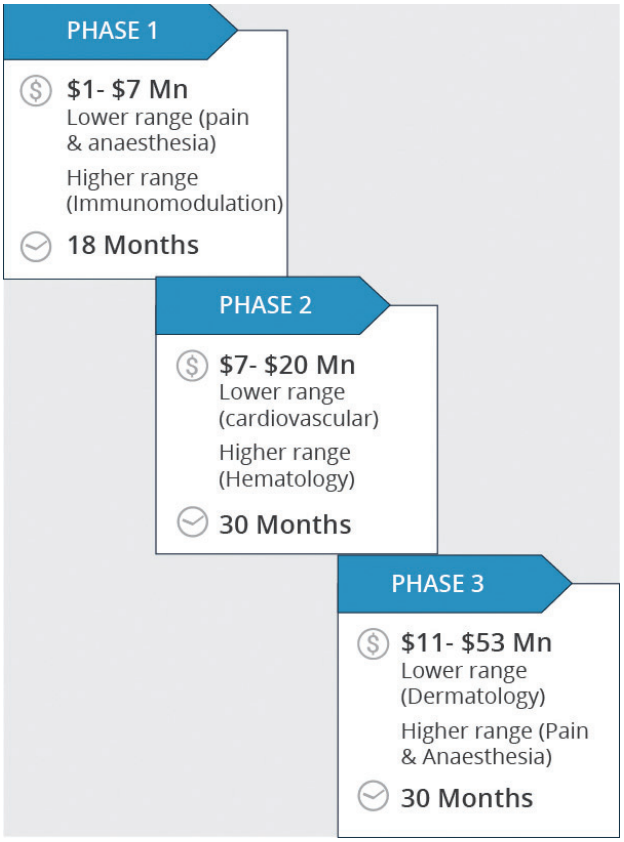
Clinical trials are characterized by significant challenges, with respect to schedule delays and cost overruns. Some industry statistics are given below:

- More than 80% of clinical trials experience delays ranging on average from 1 to 6 months, costing companies upward of $35,000 per day, per trial.[1]
- A mere 10% of trials are completed on time.[1]
- Only 14% of clinical financial planners are highly confident in their budget forecasts.[1]
- The variance between forecasted and actual clinical trial costs for life science companies can be as high as 16%. Acceptable variance range is 5% to 10%.[1]

Data-driven decisions offer higher potential in controlling the schedule and cost drivers, thus enabling reduction in schedule and budget variance. This article explores an approach for how sponsor's operational data, coupled with syndicated data and Real World Evidence (RWE) data, can enable predictive analytics on clinical cost drivers using a clinical big data and Machine Learning (ML)-enabled platform. The predictive clinical cost drivers can be used to create adaptive clinical financial budgets that include baseline spend, actual spend and projected expenses. This approach also provides details on automating the budgeting of the clinical trial financials based on trial assumptions and re-budgeting based on revised trial assumptions (as part of trial execution).

This article is composed of multiple sections. Section 1 pro-

FIGURE 1



Cost Ranges & Schedules for Trial Phases[2,3]

vides an overview of cost categories and introduces cost drivers, which are foundational for the forecasting approach. Section 2 introduces the forecasting approach on the cost drivers. Section 3 provides a high-level overview on the model's functional and technical details. The final section (section 4) reviews overall solution components.

SECTION 1: DRILL DOWN ON CLINICAL TRIAL COSTS

Figure 1 indicates the cost ranges and average schedule for various trial phases across multiple therapeutic areas.

The key cost categories, with percentage ranges and relative variance, are provided in Table 1 (patient recruitment and retention, clinical procedure, site administration and site monitoring, and site management accounts for approximately 60% to 80% of clinical trial costs).

Forecasting of the costs associated with each category involves multiple levels of decomposition for each cost category against cost groups and cost line items. A typical sponsor budget can be decomposed into cost group/account group, and cost group can be further decomposed to cost line items. Cost line item is typically associated with one or more measure items. An approach to financial prediction is to develop a forecasted model, which provides a baseline forecasting model for each measure item based on the measure item's predictor variables. Table 2 (a snapshot of a trial overall budget) provides examples of such a measure item with the corresponding predictor variable.

TABLE 1

Cost Category	Percentage Range	Relative Variance
Patient recruitment & retention	20% - 25%	++++
Clinical Procedure cost	15% - 22%	+++
Administrative site cost	11% - 29%	+++
Site Monitoring	15% - 20%	++++
Physician	6% - 8%	+++
Data Services	1% - 5%	++

Key Cost Categories

TABLE 2

Cost Category	Cost Line Item**	Measure Item	Predictor Variable Group	Independent Variable Group
Site Monitoring	Initiation Visit	No. of approved visit trip report	Site detail variables	No. of initiation visits/site
Site Monitoring	Monitoring Site Visits	No. of approved days	Site detail variables, subject detail variables, subject visit variables, site performance score*	No. of monitoring visits/site, site performance threshold*
Administrative Site Cost	Project Management	Trial months, no. of meetings	Site detail variables, trial month details	Planned no. of meetings

* - Variables used if a sponsor is using RBM for site monitoring.
** - A typical budget will have 400 to 600 cost line items.
The above table is a snapshot of 3 cost line items.

Overall Trial Budget Snapshot

SECTION 2: CLINICAL TRIAL COST DRIVERS – FORECASTING APPROACH

Based on Table 2, a clinical forecasting approach can be created based on the following five steps:

Step 1 - Forecast all the predictor variables in each of the predictor variable groups. This will involve Machine Learning approaches.

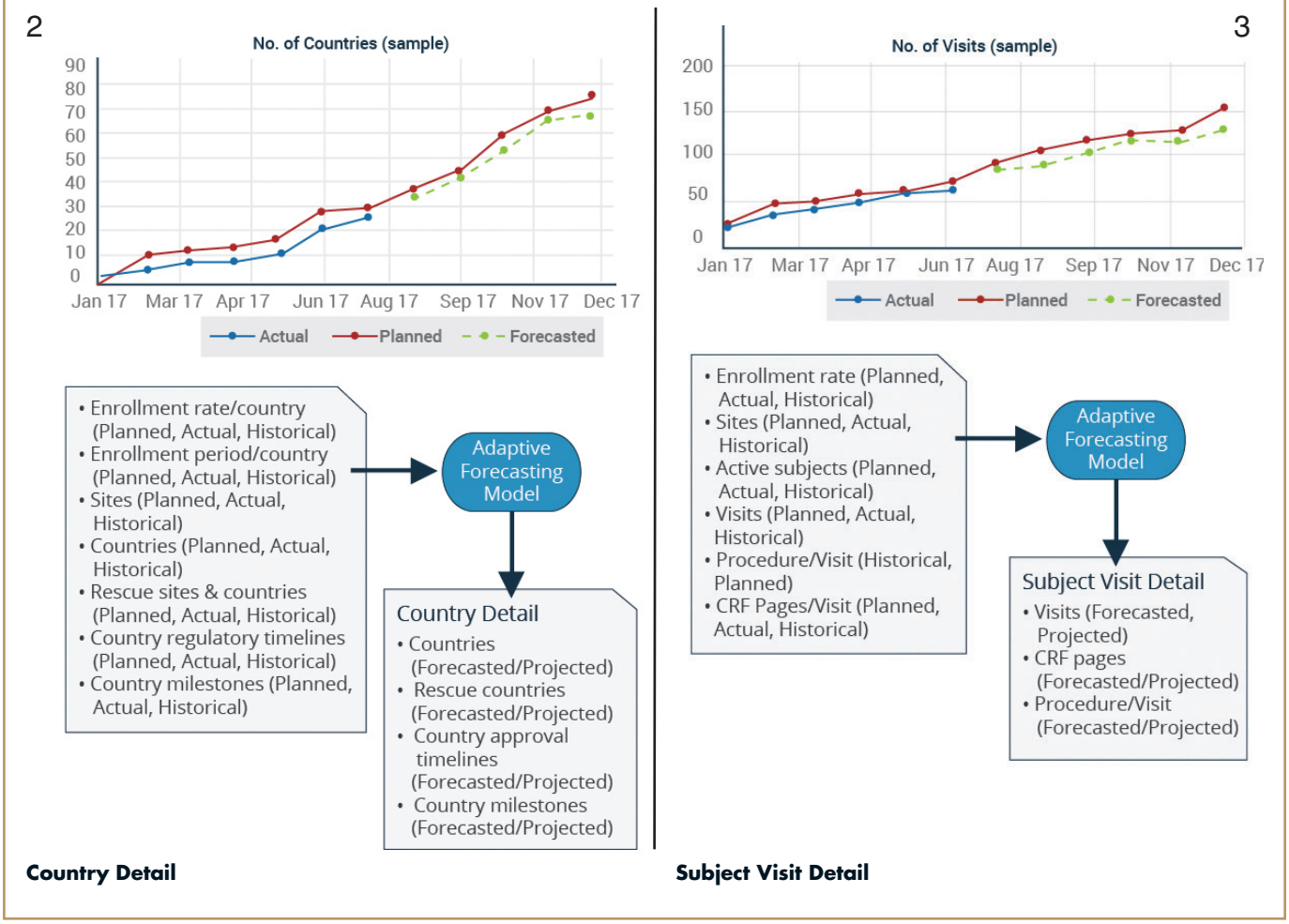
Step 2 - Using the forecasted predictor variables and independent variables, calculate measure item. This calculation will be directly arithmetic in nature.

Step 3 - Using the negotiated cost for each measure item (in case of outsourced trials) or historical cost adjusted (in case of in-house trials), calculate cost for each individual cost line item. This can be aggregated for all the cost-like items in a cost category, and further aggregated to get the budget forecast.

Step 4 - Feed the model with the actual values for the predictor variables (as the trial progresses) to create projected values of predictor variable (for the remaining trial period).

Step 5 - Continuous learning of the model based on the variance between the actual values and baseline forecast and its updated projected forecast.

FIGURES 2 & 3



If all the cost line items are analyzed as per the Table 2, a list of predictor variables can be collated to build the forecasting model. Top list of predictor variables are typically associated with country details, site details, subject details, subject visit details, and trial month details. The forecasting approach using these predictor variables enables building a dynamic and continuous learning system that can be improved based on available study data. Multiple models are necessary based on the combination of therapeutic area/indication for higher levels of accuracy.

A representation of some of the model input and predictor variable details are provided in Figures 2 and 3.

SECTION 3: MODEL FUNCTIONAL & TECHNICAL OVERVIEW

This section goes into functional and technical details of the adaptive forecasting model indicated previously.

Adaptive Forecasting Model (Functional Detail): Functional detail depends on the data sources and data processing of the data entities associated with the predictor variable. For example, in a case of predicting country approval data (a predictor variable in country detail predictor variable group), the key sources are the sponsor's country milestones data and syndicated data source containing country milestones data (for similar TA/Indication). The key inputs are country milestones (Planned, Actual, Historical) from the sponsor and syndicated sources, and the output is country approval data (Forecasted/Projected). Some of the pre-processing steps include identifying prior milestones, forecast of the prior milestones, correlation of prior milestones, and forecast of the country approval data based on the correlation factors and prior milestones. Based on the actual data (after completion of prior milestones), the model will be re-forecasted for completed prior milestones to provide new projected country approval date.

In another example of predicting first patient enrolled date for a particular site (a predictor variable in subject detail group), the key sources are sponsor operational data, claims data, registry data,

and syndicated data. The key entities are site enrollment detail (Planned, Historical), patient population (Historical/Current) and competing trials, which are extracted from claims, registry, and sponsor operational data. Some of the processing steps include identifying patient population based on claims data, co-relation of enrollment lead time (first patient) with factors such as site distance, number of trials/sites, site experience. An initial forecasting model can be developed to forecast country approval data using the aforementioned features and using the current population to forecast the country approval data. Similar to the previous example, the model will reforecast using actual details of prior milestones.

Adaptive Forecasting Model (Technical Detail): The technical approaches with respect to some of the models that can be used for clinical cost driver forecasting are in Table 3 below:

TABLE 3

Model	Considerations
Deep Learning/ Long Short Term Memory Network	• Prediction to happen at every time step and a feedback loop for the next time step to adjust next prediction • Inference obtained in previous time step is fed back to initialize hidden state for the next inference • Model explicitly uses conditional probabilities and prior and posterior probabilities
Regression - Supervised Machine Learning Algorithm	• Considers Dependent Variable as some function of other features (Independent Variables) • Fit a regression type of supervised Machine Learning model like Random Forest, XG Boost, or ensemble the models
Time Series Models	• Similar to regression but applicable for longer duration studies where cyclic trends occur • Fit a time series data using Deep Learning model(s) to train for each time step

Models for Clinical Cost Driver Forecasting

SECTION 4: SOLUTION OVERVIEW

Building a dynamic forecasting model for improved accuracy on clinical budgeting and costs involves data ingestion from multiple sources, data quality and harmonization, aggregation, and metrics generation. Saama's Life Science Analytics Cloud (LSAC) for study planning enables protocol optimization, investigator site selection, and patient identification. This section gives an overview of solution components and features. Figure 4 and Table 4 depict some components and features to look for when evaluating such solutions.

A brief description of the aforementioned components are provided below.

Source Layer: The source layer is enabled by intelligent adapters. These adapters are enabled to pull in data and meta-data near real-time for standard EDC and CTMS industry products. It also uses adapters for pulling in clinical data (views) from leading CROs. The adapters include intelligent file watcher utility to pull third party files from drop zone and do metadata checks. The source layer contains the ability to configure file level checks and remediate file loading issues. The layer also supports configuration to support both incremental and full load of clinical operational data.

Data Quality: Data quality (DQ) is based on a library of data quality rules for management of structural and business integrity data quality checks. The data quality module enables self-service functionality to perform data profiling and to create new DQ rules. It also enables remediation of source data in case of data quality issues.

Data Harmonization: The data harmonization module enables users to set up harmonization rules for harmonizing the operational data from multiple sources. The harmonization rules establish the ranking of the source attributes to be matched in a common data model. Based on the source data and the ranking rules, source data gets harmonized into the common data model.

Common Data Model: The common data model (CDM) is made up of two sub-components. The first is a canonical model to standardize the integration layer. This model is a flat staging layer model based on clinical operational subject

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areas. It enables automated mappings from landing to canonical model. The second sub-component is the consolidated operational data store. This store consolidates all raw operational data in to a single common data model. It enables both standard CDM and supports sponsor-specific CDM extensions. It also supports data versioning and full process and data traceability (landing to CDM). The data access to the common data model is enabled through fine grained access control (column, row, value level access).

Metrics Rules Management: Based on industry standards for clinical operational metrics (MCC, Transcelerate), the metrics engine allows an out-of-the-box library and also allows users-defined metrics. The Metric library enables users to set their own metrics definition to create a custom metric in the analytics layer.

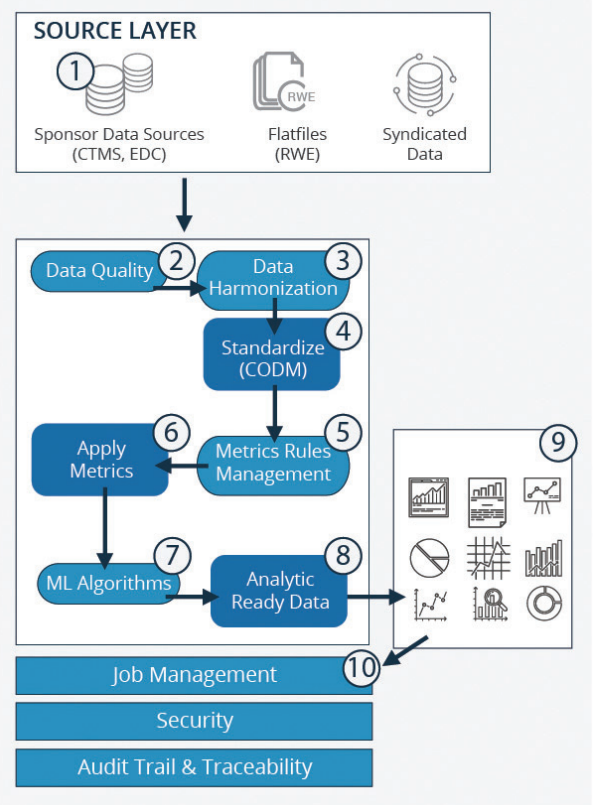
Metrics Engine: The metric rules are used to create metrics in the analytics layer from data from the common data model. The metric engine can be scheduled to execute on demand or on schedule to develop metrics data through incremental or full load of data from the common data model layer.

ML Algorithms: The solution allows machine learning training on historical data to predict KPIs on the current trials. For example, based on historical country approval milestones, a machine learning model to predict country approval date for a study can be developed. This model allows reviewing the model accuracy on a continuous basis, to retrain and to redeploy for improved accuracy.

Analytics Layer: The analytics layer is a consolidation of all conformed data into a single analysis dataset layer. It contains both operational KPI created through KPI library and predictive KPI created through machine learning libraries. It also supports storage of KPIs, which can have calculation variation depending on study hierarchy.

Visualization: The visualization includes canned reports, exploratory analysis reports, RBM reports and machine learning-based dashboards. The capabilities of threshold

FIGURE 4



Solution Components & Features

TABLE 4

S.No	Component	Key Features
1	Source Layer	Pre-built source adapters for near real term data ingestion
2	Data Quality	Rules based and machine learning based data quality for structural and business data quality checks
3	Data Harmonization	Enables rules management to construct single golden record (for operations data)
4	Common Data Model	Common data model to aggregate operation data across multiple subject areas
5	Metrics Rules Management	Self-service based metrics engine to configure business rules for KRI creation
6	Metrics Engine	Metrics Engine that calculates metrics from common data model
7	ML Algorithms	Library of machine learning algorithms to create models
8	Analytics Layer	Layer that contains both the metrics, models and model output
9	Visualization	Layer that shows model output and operational visualizations (canned/ exploratory)
10	Foundational Features	Solution foundational features that enables job management, user and data security and compliance with validation and regulatory requirements

Solution Components & Features

management, alerts, tasks and notification management are also part of this module. This module supports operational reports on key standard operational KPIs with interactive filters. It enables users for BYOR (bring your own reporting tool), and developed external reports can be enabled for access. Visualizations rendering to a user is based on the data access security model.

Foundational Features: The system allows both system workflows (e.g. data transformations) and business workflows (e.g. DQ issues or KPI breach). It abstracts the complexity of open source components through a self-service orchestration layer. All the changes to the data layer supports audit trail and data traceability across all layers.

The features of the solution also include a virtual assistant, which allows conversational experience on key intents (topics) for a scope of operational subject areas. It enables users to view graphs on demand (on known intents) to provide details on a conversation. It supports continuous training of the virtual assistant for accuracy improvement, with respect to responses from the virtual assistant. The virtual assistant is trained on the common data model. The roadmap includes a plan to support voice-based conversations in future. ◆

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BIOGRAPHY

Srini Anandakumar is the Senior Director of Clinical Analytics Innovation at Saama. He is responsible for leading the solution development for next-generation clinical repositories based on Big Data and AI. He has more than a decade of experience building clinical analytics solutions for enabling both analytics and submission pathways. His experience includes product management and consulting in the clinical R&D space. His current passion is to explore the possibility of AI applications to bring in efficiencies in clinical development.

Drug Development
EXECUTIVE

Oskar Gold

Senior Vice President, Key Account Management & Marketing/ Corporate Communications

Vetter Pharma International GmbH

Vetter: Insights on Insourcing Versus Outsourcing in the World of Injectable Manufacturing

Aseptic manufacturing is a key stage in drug development and commercialization, requiring a careful approach and attention to detail. Once a pharma or biotech company completes the drug discovery phase, how does the drug get packaged into its drug delivery system, passing successfully through clinical manufacturing and into the market for commercial supply? Does the strategy differ for small-, medium-, and large-size companies? What are the factors that must be considered? Drug Development & Delivery recently interviewed Oskar Gold, Vetter's Senior Vice President Key Account Management and Marketing/Corporate Communications, to discuss these questions, and offer his insights as to why careful thought and consideration of different criteria must be applied.

Q: Can you please update our readers about your company and what service portfolio it offers?

A: Vetter is a globally operating solution provider for large and small pharma and biotech companies and is active in the field of injectables. As a contract development and manufacturing organization, commonly referred to as a CDMO, our portfolio spans services beginning in early development support, including clinical manufacturing, on through to commercial manufacturing and secondary packaging services. Headquartered in Ravensburg, Germany, we operate production facilities in Germany and the United States. We currently employ approximately 4,400 employees who are

"A major advantage of outsourcing anything that is not part of their core-competency is that the sponsor company can be free to focus its energy on executing development project expectations of investors and shareholders."

experts in their respective fields, which enables us to provide the high quality necessary to be a successful and trusted partner in this niche market.

In the field of aseptic manufacturing of prefilled drug delivery systems, we have more than 35 years of experience that includes support for dozens of market approvals for new injectable drugs of our customers. Because we have been dealing with complex compounds for quite some time, our innovations in both systems and processes were always decisive for our company's success and remain so today.

Q: Can you give us your insight into how a business model for aseptic manufacturing might be structured for a small company, like we see many of them in today's biotech corridor?

A: Overall, the industry has seen an increase in competition that has led to the need for high flexibility in the manufacturing process, regardless of the size of the company. While biologics, such as antibodies, peptide conjugates, and vaccines are very promising development fields, the ever-increasing R&D spending and price pressures to develop them have put a burden on the industry. This is particularly true for the cash-strapped small biotech companies. To be successful in aseptic manufacturing, companies need extensive experience in current Good Manufacturing Practice (cGMP) and require site approval from regulators. The lack of in-house specialized expertise and expensive equipment needed to perform drug development and manufacturing often makes it more feasible for smaller companies to contract out most, if not all, of the development and manufacturing work once the discovery phase and preclinical development of their active compounds has been completed successfully.

Q: How about medium-size pharma and biotech companies? Is the model for companies like these any different?

A: The answer to this question is not as simple. We find that many mid-size companies, unlike their smaller counterparts, do have the financial resources for realizing their drug development and manufacturing in-house, creating any needed expertise and acquiring necessary equipment. But often, they do prefer outsourcing as well. Throughout the past decade or more, we have seen a number of leaders in the pharma and biotech arena that have had great success with a small number of expensive compounds and therapies. Much of this success has been achieved by concentrating all of their resources on R&D and marketing while outsourcing the remaining process steps. This includes contract manufacturing for both clinical and commercial drug products. A major advantage of outsourcing anything that is not part of their core competency is that the sponsor company can be free to focus its energy on executing project and progress expectations of investors and shareholders. Resources can then be applied to the creation of a multi-candidate pipeline to help mitigate risk failure in the clinical phase. However, they must be ever-more vigilant since the use of multiple suppliers means that each contract service firm has to be formally audited to allow for the cGMP process and regulatory submission. However, maintaining in-house resources is impractical since these capabilities, quite often, cannot be utilized completely and, thus, are not cost efficient. Therefore, for the medium-size company, realizing outsourcing as a way to reduce and keep the number of strategic, not tactical, partners to a minimum can offer an encouraging roadmap to supporting its daily operations.

Q: That brings us to the question about large companies. What approach should they be taking?

A: It is probably in the best interests of large pharma and biotech companies not to have a single, fixed strategy. This seems contrary to what I recommend for smaller and medium-size companies and, actually, it is. Several years ago, we had seen a number of these large companies achieve major global manufacturing capabilities through activities like mergers and acquisitions in addition to organic growth. If you ask them what are the other reasons they have for insourcing, they often will respond that it enables them maintain 100% control over the process. However, striving for quality can also be achieved through a common quality understanding between sponsor and partner. This requires a partner that stays abreast of new and emerging regulations and is able to meet ever-increasing quality standards. Often cooperating with a CDMO provides a sponsor company access to the latest state-of-the-art manufacturing technology. For reasons of confidentiality, some of these companies prefer contracting independent partners with no own products on the market, so as to avoid any potential conflicts of interest. Another common model is using CDMOs to serve as a second production source, often to enable the supply of a drug product to specific areas of the world.

There are a lot of industry leaders that make every effort to balance insourcing and outsourcing activity. Achieving this balance helps them secure supply, optimize performance and flexibility, as well as minimize risks.

Q: What then, in your opinion, are the key advantages for both insourcing and outsourcing?

A: If a company has all the necessary capacity available for realizing the drug manufacturing in-house, then this might be a logical approach. It allows them to remain completely independent from suppliers, keeping 100% control over their manufacturing and supply chain. Even the unlikely case of a potential leaking of intellectual property (IP) is kept to a minimum.

But, outsourcing does have a couple of advantages as well. This is often the case when the needed efforts to achieve global quality consistency across sites are equal to, or even more challenging as compared to contracting with an external CDMO partner.

Economic efficiency is another important benefit. Professional suppliers that are committed to a customer's business will always remain up-to-date in terms of regulations and technology. They will also have skilled employees and well-maintained sites and hardware. These elements of manufacturing are very expensive for a company to maintain on its own. For these reasons, having a supplier that has long-term expertise and state-of-the-art equipment to realize manufacturing in an economic manner is an attractive pathway for many pharma and biotech companies.

Q: Any final thoughts about the "right manufacturing strategy" for companies of any size to take?

A:Within the industry, different faceted forms of outsourcing are certainly the trend. According to Eric Langer's BioPlan Associates 15th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production 2018, companies are weighing their outsourcing versus insourcing options, with a longer-term perspective. While some companies are geared to keep capital costs low, including through outsourcing, others see strategic company value by developing and increasing their in-house manufacturing competency.

For us as a CDMO, one of the valuable survey information mentioned was that 67% of respondents indicate that fill/finish is currently their primary outsourced activity.

At the end of the day, it is the pharma or biotech company that has to make a decision concerning insourcing versus outsourcing, based on the parameters outlined earlier. Depending on the availability of in-house capabilities, a strategy that combines both insourcing and outsourcing will often lead to the necessary flexibility and reliance on third-parties. This strategy also affects the relationship with a partner that is based on long-term planning and cooperation. Long-term strategic partnerships will continue to add experience and knowledge to both sponsor and partner – a crucial benefit when navigating in an increasingly competitive and challenging market environment, with only little room for failure, or for getting a second chance following wrong initial decisions. ◆

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Special Feature

Outsourcing Analytical Testing: The Gateway to Drug Manufacturing

By: Cindy H. Dubin, Contributor

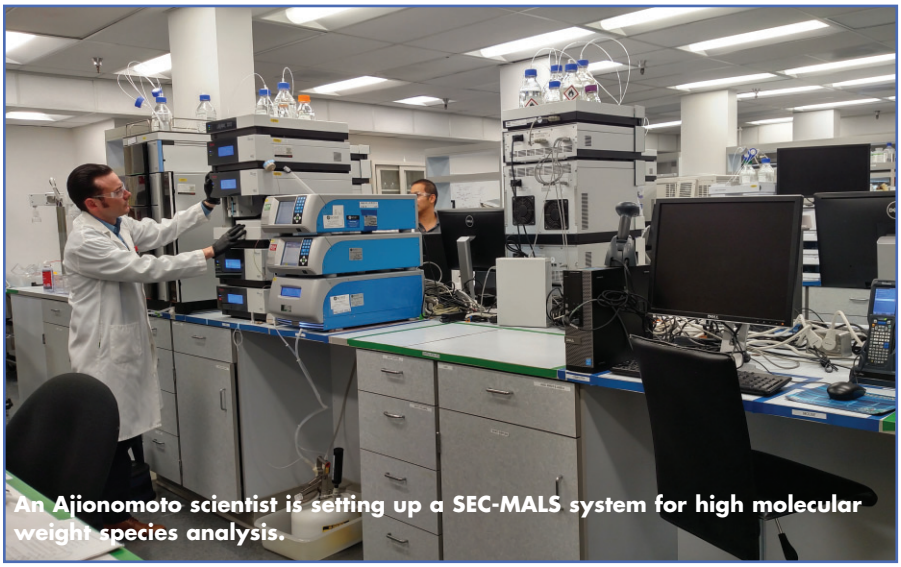
Pharma's reliance on Contract Development and Manufacturing Organizations (CDMOs) to provide method development, process validation, and stability storage testing has experts predicting that the global analytical testing outsourcing market will reach $9.6 billion by 2025.[1] But they also expect that CDMOs will be challenged by more rigorous requirements put forth by pharma customers.

"In the future, a major challenge for CDMOs from an analytical testing perspective is the increasing cross-section of drugs designated as highly potent active pharmaceutical ingredients (HPAPIs) – to which both small and large molecules are susceptible," says Cheryl Johnson, Commercial Development Manager of Biotechnology at Alcami. "HPAPIs require special containment procedures, engineering controls, and a culture of diligence with respect to individual safety. Each part of the testing process must be handled with careful consideration to minimize potential for exposure."

Another challenge, says David Exline, President of Gateway Analytical, is that analytical labs will need to ensure that their systems and processes meet data integrity standards required by clients. "Significant opportunity exists to provide a fully GMP-compliant analytical testing solution that encompasses analytical analysis, as well as leverages technology such as new instrumentation and databases for more accurate data mining and trending. This also creates the greatest challenge in that outsourced analytical labs must ensure that their systems and processes meet the data integrity standards that are required by our customers."

Ananda Seneviratne, PhD, Director, Analytical Technologies, Ajinomoto Bio-Pharma, agrees: "Analytical assays are the gatekeepers to the entire drug product manufacturing process. Thus, analytical data are heavily subjected to regulatory scrutiny from pre-clinical to commercial."

Cambrex High Point's quality control laboratory follows strict guidelines in performing testing held to the highest standards.



An Ajionomoto scientist is setting up a SEC-MALS system for high molecular weight species analysis.

The pros agree that contract labs must continue exploring new and different strategies, technologies, and testing to provide competitive and cost-effective services. This annual report in *Drug Development & Delivery* magazine helps illustrate some of those technologies, services, and strategies offered by leading analytical labs and CDMOs.

Ajinomoto Bio-Pharma: Customized Analytical Programs to Unique Molecules

Ajinomoto Bio-Pharma, a CDMO, offers a range of analytical services for method development, method transfer, and phase-appropriate method qualification or validation combined with or without fill-finish operation services for the biopharmaceutical industry. The CDMO also offers a variety of analytical technologies for ADC characterization, particle and high molecular weight species analysis, and characterization.

"Our analytical programs satisfy regulatory requirements and dedicated analytical scientists customize phase-appropriate analytical programs to the specific needs of unique molecules, delivering a comprehensive understanding and characterization of the molecule for each stage of development and commercialization," says Ananda Seneviratne, PhD, Director, Analytical Technologies, Ajinomoto Bio-Pharma.

Reference lots or standards are incorporated throughout the analytical program and are utilized as controls for assays used during the development and characterization of a product. Every time a product is manufactured, Dr. Seneviratne says that scientists compare it against the standard to ensure it has comparable quality and purity.

Ajinomoto analytical scientists develop and optimize methods, and solve analytical method transfer issues. As an example, Dr. Seneviratne says an RP-HPLC method that was transferred to Ajinomoto contained an hexylammonium acetate (HAA) and 1,2-diaminiocyclohexan tetraacetic acid monohydrate in the mobile phase with a tight mobile phase pH. This method was successfully transferred from the client to the analytical technology lab, but failed during the method transfer to the QC lab for routine testing. Analysts eliminated the possible root causes and identified that the pH adjustment step using ammonium hydroxide was the root cause. Another example is an RP-UPLC method transferred to Ajinomoto showed low sensitivity for 2 analytes. To minimize the assay's variability, the assay was run using the same model and type of RP-UPLC instrument used in development of the original method at the client's site. "Our analysts utilized another model and type of UPLC and used the same mobile phase column to identify that the root cause was the hardware and not the chromatographic conditions or the sample matrix," he says. "Once the root cause was identified, our analysts were able to fix the hardware and transfer the method to the QC lab."

Catalent Pharma Solutions: Adapting Analytical Services to Meet Regulatory Requirements

Catalent offers a variety of analytical testing to support preformulation, formulation, and drug product characterization – all complying with multiple compendial requirements. Capabilities span from full method development to GMP validations for both raw materials and finished products, both small and large molecule analysis, including highly potent compounds. Analytical services are adapted to meet the regulatory requirements at each phase of development to save time and costs associated with development. The company's focus is on early characterization of the molecule and prototype formulations to allow for data-driven selection of the optimal formulation to progress to clinic.

As a full-service hot melt extrusion solution provider, Catalent developed and optimized formulations for one customer's product, says Ketki Patel, Senior Manager, Quality Control & Analytical Product De-

One of Catalent's development laboratories.

velopment, Catalent. Catalent developed and validated methods, supported product selection activities, and completed full ICH stability assessment, resulting in successful submission and commercial launch – the product has since been approved in different parts of the world.

From its own global network of analytical centers, Catalent's capabilities include liquid chromatography, gas chromatography, mass spectroscopy, NMR, laser diffraction, DSC, and XRPD. Quality control tests are also offered, and Catalent supports impurity characterization and identification, including elemental impurities (ICP-MS) and extractables and leachables testing, full microbiological evaluation, and wet chemistry testing. Catalent is experienced in performing *in vitro* bioequivalence studies and executing comparative dissolution studies to understand product release profiles, says Steven Winling, Technical Specialist, Softgel Product Development, Catalent.

Gateway Analytical: Undertaking Stringent Particulate Characterization

Gateway Analytical was established to address the growing need of GMP-compliant foreign particulate characterization testing in pharmaceutical product development and manufacturing. Over the past two decades, non-conformance issues related to foreign particulate investigations has been met with more stringent regulatory oversight and importance. In today's regulatory environment, it has become critical to not only understand the identification of these types of foreign particulate but also to understand the source and impact on product.

A pharma company may opt to outsource analytical testing as it relates specifically to particulate investigations because non-conformance investigations can be time consuming, says David Exline, President of Gateway Analytical. "The ability to provide identification and source determination for foreign particulate matter (FPM) during a non-conformance investigation has been critical to customers. It is typical for a lot/batch of product to be put on hold until an investigation has been completed into the source of FPM and the impact of foreign particulate in the drug manufacturing process. This can be an expensive undertaking and have significant cost implications to the manufacturer if not done correctly or if the cGMP analysis has not been completed correctly."

SGS: A Range of Methods for Product Failure Investigations

In the evolving area of biopharmaceuticals, expertise with earlier phases of the development pipeline and a clear understanding of the regulatory expectations are critical. SGS maintains a diverse portfolio of analytical testing services with laboratories in North America, Europe, and Asia. Services include extractables and leachables, biologics characterization, biosafety, bioanalysis, analytical chemistry, and microbiology. On-time delivery is significant for these testing services and can be tied to short-term capacity constraints. SGS mitigates this issue by maintaining an integrated network of laboratories with the ability to react quickly to unforeseen capacity demands.

SGS also performs product failure investigations. Such programs can be challenging and complex, requiring instrumentation and expertise from a diverse selection of disciplines. One such investigation was initiated after particulates appeared in a biologic final drug product. "In such instances, there can be many potential explanations ranging from those related to the API, the excipients, the container system or a combination of these," says Mark Rogers, PhD, SGS Global Technical Director. In this study, the analytical strategy was particularly demanding, he says, as the particulates appeared insoluble in all but the most extreme solvent conditions. Initial analysis by FTIR indicated the particle's non-proteinaceous nature, which was confirmed by SEM-EDX, MFI, and ICP-OES. Complementary data obtained from a range of SGS methodologies, provided clear evidence that the particulates were created by unexpected delamination of the product container. "This information allowed the client to re-evaluate

West Chester, PA, laboratory of SGS.

the container system, and assign accountability," he says.

Alcami: Customizing Programs to Meet Accelerated Product Timelines

Alcami is a CDMO that offers fully integrated, comprehensive analytical testing to support technologies for every stage of development. Its laboratory services platform is comprised of analytical testing and development services for small molecule and biologics drug products, as well as specialized offerings such as elemental impurities, abuse deterrence, and extractables and leachables. In addition, formulations development scientists address challenges related to new chemical entities.

Because Alcami's portfolio touches on all phases of development, advancements in technology and regulatory requirements are closely monitored. "The industry has changed drastically over the years and analytical testing has evolved with it," says Cheryl Johnson, Commercial Development Manager of Biotechnology, Alcami. "Control of impurities, excipient selection, and packaging safety are a few examples where increased awareness has led to higher expectations of analytical testing capabilities to satisfy regulatory requirements."

Given that the manufacturing of biologics requires characterization of the drug substance beyond the typical impurity profile of a small molecule drug product, biologics are particularly susceptible to changes in requirements. "Thus, the demand for higher resolution, sensitivity, and accuracy of classic techniques such as chromatography, mass spectrometry, and electrophoresis is an analytical imperative," says Ms. Johnson.

The evolution of analytical testing is not limited to specific techniques or instrumentation. It also applies to regulatory guidelines such as data integrity, infrastructure like electronic notebooks, and automated sample tracking systems for chain of custody. Regulatory agencies expect continuous recording of the materials so that their handling can be recreated during an audit or investigation. Tolerance to this high level of scrutiny is a key indicator of a robust analytical testing portfolio.

Ms. Johnson illustrates how Alcami's regulatory expertise was an advantage for a client that needed additional support to meet rigorous FDA requirements during an NDA review to get the product to market. Alcami's Extended Workbench solution helped the client address accelerated clinical trial and commercial launch timelines by providing a full-time equivalent (FTE), comprehensive, and customized service program. The program was designed for release and stability testing of batches for specific analytical testing requirements.

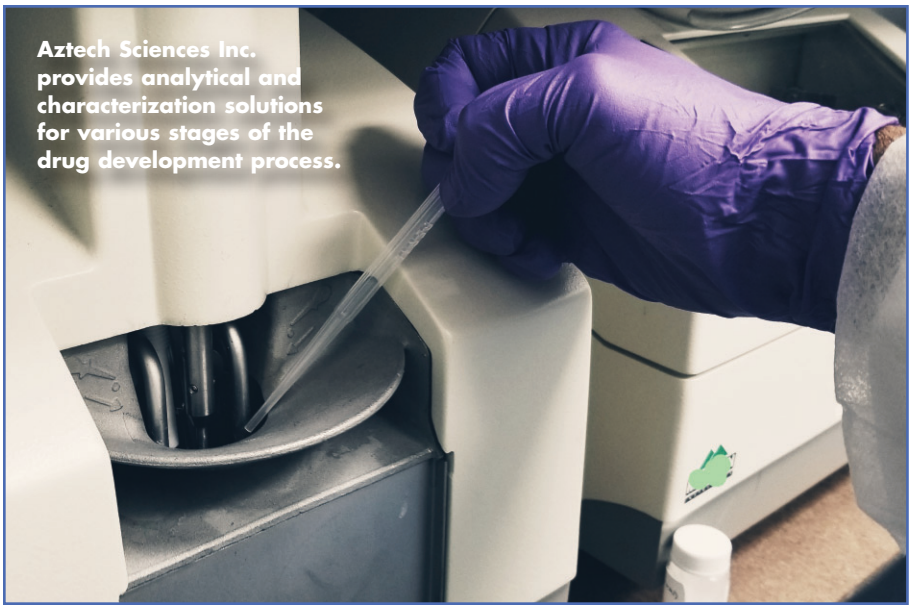
"With dedicated Alcami staff to the project, it granted the client additional flexibility, freedom, and consistent control over their outsourced laboratory needs, and the product has been launched nationwide," says Ms. Johnson.

Aztech Services Inc.: Risk-Based Management Approach to Analytical Development

Aztech Sciences Inc. offers development and testing solutions for pharmaceutical analytics, preformulation, and formulation, analyzing pharmaceutical raw materials, formulation prototypes, drug delivery systems, and finished products.

Alvin Persad, President of Aztech Services Inc., explains that the current climate for outsourcing organizations has become more challenging in the past few years as a result of increasing demands in quality initiatives and cost-effective operations. To address these challenges, Aztech Sciences Inc. works closely with customers to identify key objectives and goals to provide more efficient services and strategies. "Our risk management-based approach for analytical development is in resonance with the contemporary regulatory guidelines to ensure our analytical services exceed high standards while aligning with product milestones and timelines," he says.

As an example, Aztech Services Inc. is currently working with an early-stage drug discovery organization that is continuously exploring and evaluating various



Aztech Sciences Inc. provides analytical and characterization solutions for various stages of the drug development process.

formulation drug delivery systems to achieve the desired *in vivo* exposure suitable for preclinical toxicology and preliminary efficacy. "By providing continuous analytical development and formulation vehicle characterization, the client's analytical requirements are met while allowing the pursuit and evaluation of other aspects of preclinical challenges, leading to a prospective first-in-human (FIH) program," says Mr. Persad.

Cambrex: Navigating R&D & Regulatory Pathways

Cambrex's facility in High Point, NC, specializes in clinical phase active pharmaceutical ingredients (APIs), mainly in the pre-investigational new drug application (IND) through Phase 2. The company provides analytical R&D support, QC release, and stability capabilities to small virtual companies and large pharmaceutical multinationals.

The High Point site follows ICH Q7 guidelines, as well as other regulatory guidances, and is fully cGMP compliant. "Changes to the analytical landscape over the past 10 years have included the replacement of USP<231> Heavy Metals with the new USP<233> Elemental Impurities testing, and the growing interest in the determination of potential genotoxic impurities (PGI)," says Mark Shapiro, Director, Analytical Research & Development Cambrex. "In the PGI field, we have successfully developed methods capable of quantitation at very low level (sub-parts per million)."

Cambrex has addressed these industry changes through straightforward approaches, including the installation and qualification of triple quad mass spectrometers, as well as ICP-MS instrumentation. Additionally, Cambrex expanded capabilities in identifying unknowns, installing electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) sources to triple quad LC-MS instruments, as well as GC-MS instruments with both electrospray ionization (EI) and chemical ionization (CI) capabilities.

Relying on its technical knowledge and testing capabilities, Cambrex High Point recently manufactured drug material for a customer for which an HPLC assay and impurity testing method had been developed and qualified at another CMO lab, and for which QC release and stability were performed. "Our studies and work showed the HPLC method to be insufficient to determine a positional isomer of the drug compound that very closely co-eluted with the main compound," explains Mr. Shapiro.

A new, more specific test method had to be developed and qualified. This process was fairly straightforward, but, as the material underwent stability storage, the assay values for the main compound were observed to be rising over time. Mr. Shapiro says this was because of the previously unrecognized hygroscopic nature of the material (both standard and sample), which was not accounted for in the assay calculations. Upon discovery of this, appropriate changes to the method, including determination of water content of the standard at time of use, as well as modifications to the assay calculations, provided sufficient course correction to the stability, and allowed the material to successfully continue on an extended stability regimen.

From a regulatory standpoint, Cambrex mentors clients by helping them navigate the complex waters of regulations, while meeting the phase-appropriate needs of the drug compound. Cambrex has recently announced an expansion program for the High Point site, and, Mr. Shapiro says, the challenge will be to ensure this growth aligns with the continuing changes to the regulatory landscape for the analytical demands of the earlier phases of the pharmaceutical life cycle as well as more broadly across the API field.

Charles River Laboratories: A One-Stop-Shop for All Things Analytical

Charles River Laboratories evolved from a supplier of laboratory animal models to a global, fully-integrated, early-stage contract research organization (CRO), pro-

viding products and services that support drug development. As outsourcing has become more common across the pharmaceutical and biopharmaceutical industry, there has been a greater demand for the "one-stop shop." In line with this, Charles River has expanded capabilities and capacity through strategic acquisitions and expansion of its global portfolio.

From the analytical side, Charles River has worked with several companies in addressing drug development challenges. "Our analytical and formulation teams have resolved insolubility problems and stabilized molecules for long-term storage, or successfully identified product- and process-related impurities that would have caused potential safety issues and also worked with clients to modify the up-stream manufacturing process," says Mario DiPaola, Senior Scientific Director, Biologics, Charles River.

He says that looking toward the future, there are several opportunities within the analytical space of drug development. Molecules in clinical development are becoming more complex, for example antibody-drug conjugates (ADCs) or bispecific/trispecific antibodies, and their analysis requires more sophisticated analytics. For ADCs, these analytics include the mapping of the drug conjugation sites and determination of occupancy at each site, and the analysis of impurities that include free drug, free linker, and free drug-linker complex. Similarly, bispecific and trispecific antibodies require unique biological/binding assays to confirm bispecific and trispecific functionalities.

There are also new therapeutic modalities including gene therapy and cell therapy that require novel analytics for characterization, product release, and determination of stability.

Tuning instrumentation for quantification of leachables (Next Breath, an Aptar Pharma Business).

"As more products and more therapeutic modalities enter the clinical evaluation phase, there will be the need for more creative analytical methods that will address the needs of these new product types, while at the same time decreasing the testing cycle time, so that products can be tested and released for use within days rather than weeks or months," says Mr. DiPaola.

Next Breath, an Aptar Pharma Business: Evolving Expectations for Drug Delivery Systems

As pharmaceutical drug products increasingly utilize delivery systems for targeted administration to the patient, regulatory bodies are asking sponsors to demonstrate reliability, safety, and to address the patient's ability to utilize the device. "FDA's Combination Drug Product Guidance seems to be driving the demand for scientific evidence of performance," says Julie Suman, President of Next Breath. "However, this is happening earlier in the development cycle, as early as an investigational submission."

As an analytical service provider, she says that Next Breath, an Aptar Pharma business, can counsel sponsors on these changing regulatory expectations and help develop a proactive plan of action. "In some cases, regulatory questions are unexpected and require a rapid response," she says. "This is where expertise in these specialized areas, such as extractable and leachable or spray characterization and deposition, can expedite delivery of results."

A case study that illustrates this rapidly changing environment is a study that Next Breath performed for a sponsor to quantify leachables from an ophthalmic product. The regulatory query occurred at the investigational submission phase. As the sponsor's clinical study was slated to begin, the ability to rapidly develop extractable methods and provide results to satisfy regulators was critical, says Dr. Suman. Next Breath worked with the sponsor to meet the timelines to satisfy the FDA's request. In late 2018, the sponsor received approval to initiate clinical trials.

In addition to a changing regulatory environment, another challenge is the development of new methodology, such as structural equivalence or *in vitro* models, to understand the link between the formulation, device, and the patient, says Dr.

Recro Gainesville has upgraded key analytical equipment to address clients' needs for efficiency.

Suman. "These models are used to not only facilitate process development, but also to benchmark performance. For example, in a Next Breath study performed in partnership with a large pharma company, it was shown that nasal spray deposition using nasal cast models can facilitate product development to tackle unmet needs in upper respiratory inflammation and congestion."

Recro Gainesville: Addressing Needs for Greater Efficiency in Analytical Testing

Recro Gainesville provides method development and validation services (assay, related substances, residual solvents), develops cleaning methods, conducts full ICH stability studies, and performs analytical preformulation characterization studies, such as structural elucidation, impurity profiling, solubility, pKa, particle size, and zeta potential, among others. Dissolution systems for immediate- and modified-release dissolution profile studies and physical property tests, such as hardness, disintegration, and friability, round out the offerings.

Prabhakar Reddy, Associate Director, Analytical Development, Recro Gainesville, says that speed and agility are client priorities to progress from early animal studies for dose determination to safety and efficacy studies in humans to FDA submission in ever-constricting timelines. To address clients' needs for greater efficiency, Recro Gainesville has upgraded key analytical equipment and added experienced scientific staff. State-of-the-art UPLC systems, dissolution systems with autosamplers, and SOTAX lab automation systems all contribute to faster turnaround. In addition, the FDA has been recommending the use of QbD approaches for process and product development, so Recro Gainesville recently purchased a QbD method development system to speed up method development.

Speed was particularly demonstrated in a recent project where Recro Gainesville successfully developed a single-gradient UPLC method to separate and quantitate 12 different small-molecule analytes (with widely different concentrations, polarities, and solubility characteristics) — in less than 11 minutes. During product development, to make the method more QC- and user-friendly, scientists re-developed and validated another single UPLC gradient method focused on just the two most different components, reducing the run time from 11 minutes to 5.5 minutes. In addition, they successfully validated and transferred the assay, related substances, content uniformity, and dissolution methods using automation equipment (SOTAX TPW and SOTAX AT MD), further decreasing the analysis time and cost of operations while achieving consistent data generation and reliability in the QC environment. "Investments in staff, training, and technology allow companies to provide clients with accurate and consistent analytical data so that they can get to the clinical and commercial stages much faster," says Myke Scoggins, Director, Product Development, Recro Gainesville. ◆

Reference

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BIOGRAPHY

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

DEVICE REGULATIONS

The New Medical Device Regulation & the Applicability of Article 117 to Medicinal Products

By: Louise Place

INTRODUCTION

"Those who expect moments of change to be comfortable and free of conflict have not learned their history." For many involved in the medical and pharmaceutical industries within the past few years, this quote – attributed to American historian Joan Wallach Scott – has never been more true. From the impending switch to the Clinical Trials Regulation to the implementation of the Falsified Medicines Directive, and the evolution of the Medical Devices Regulation (MDR) or the current uncertainty around Brexit in Europe, change is everywhere. With so many new developments in progress, it is almost impossible to keep track of all the required updates to procedures – with a very real risk of missing something critical.

Article 117 of the new MDR, has the potential to be one such pitfall.[1] Buried deep within the final chapter of the document, just before the annexes, is the somewhat innocuously titled Amendment to Directive 2001/83/EC. For many medical device manufacturers, this article is likely to be mostly disregarded, as Directive 2001/83/EC – also known as the Medicinal Product Directive (MPD) – has historically not been an essential part of placing a device on the market.[2] For companies whose focus is primarily on the MPD – like many pharmaceutical and biotech companies - this update may pass completely unnoticed.

This article is primarily focused with the impact of Article 117 in Europe on the combination of a drug and a device, where the primary mode of action is performed by the drug and the two products are combined in a single, integral product that is exclusively for use in the given combination and not reusable. Some examples of products that would be categorized in this combination include a single-use, disposable auto-injector or a disposable pre-filled metered dose inhaler.

DIFFERENCES BETWEEN US & EUROPE

The US and EU have very different systems for determining assessment routes for drug (or biologic) and device combinations, as shown in Figure 1.

The US refers to these products as combination products and selects a lead division with primary jurisdiction based on the primary mode of action. The other division is also consulted for the relevant aspect of the product.

In Europe, the process is slightly different because the term combination product is not officially recognized – albeit more frequently used, even in the absence of an official "status." Whilst products are still assessed based on the primary mode of action, this determines one of two primary assessment formats; either medicinal product or medical device.

THE EXISTING SYSTEM

The MPD requires evidence of CE marking when it is applicable but does not detail requirements for non-CE marked devices. Under Article 1 sub-part 3 of the Medical Device Directive (MDD), devices in which "the device and medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable" were governed by the MPD with the additional applicability of the essential re-

quirements of Annex I to the MDD with regard to safety and performance-related device features.[3]

Devices that do not meet this clear definition were governed by the MDD, unless they were in vitro diagnostic devices or active implantable devices governed by Directive 98/79/EC and Directive 90/385/EEC respectively.[4,5]

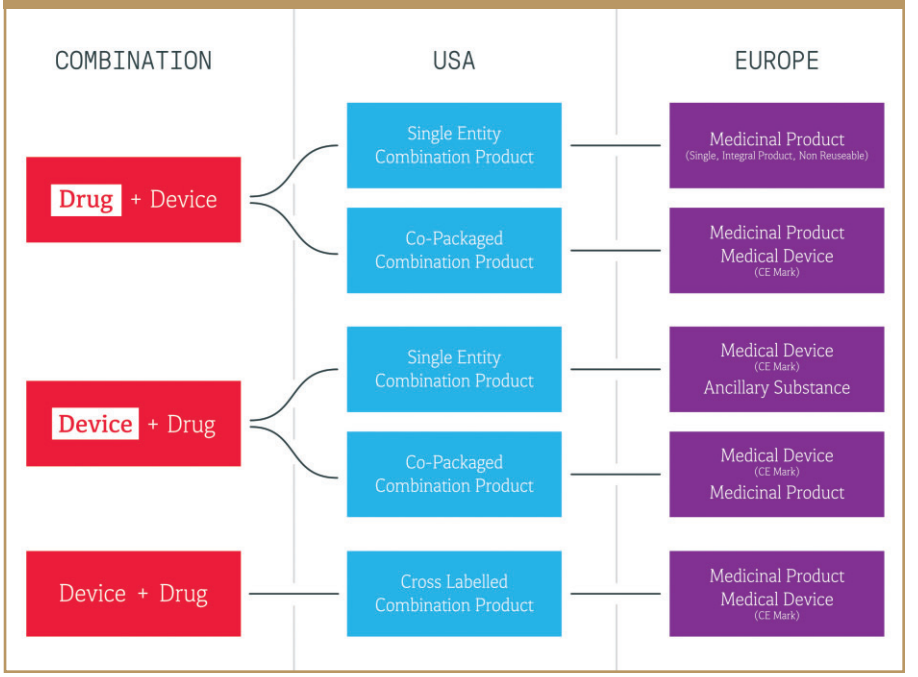
WHAT'S CHANGED?

Article 117 of the MDR legally amends Annex I, Section 3.2 point 12 of the MPD as follows:

"(12) Where, in accordance with the second subparagraph of Article 1 (8) or the second subparagraph of Article 1 (9) of Regulation (EU) 2017/745 of the European Parliament and of the Council (*), a product is governed by this Directive, the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a Notified Body allowing the manufacturer to affix a CE marking to the medical device.

If the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a Notified Body is required in accordance with Regulation (EU) 2017/745, the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a Notified Body designated in accordance with that Regulation for the type of device in question."

FIGURE 1



For many medicinal products this amendment will not introduce an onerous change as a device that is non-integral to the medicinal product will still need a CE mark with the appropriate conformity contained within the declaration of conformity.

The key element of this change applies to integrated, non-reusable products in which the drug element has the primary mode of action. In essence, the device element of a medicinal product – when integral, non-reusable, and intended exclusively for use in the given combination – needs to conform to the Annex I (MDR) general safety and performance requirements without the requirement to be regulated as a CE-medical device.

As part of demonstrating this, a Notified Body opinion must be incorporated into the marketing authorisation application for the medicinal product.

WHAT DOES IT MEAN?

With an increasing shift away from small molecule drugs toward biologics and an increased desire for patient self-administration to reduce the burden on healthcare systems, the option to combine a drug formulation with an integrated delivery device seems increasingly likely. There are some key implications of the Article 117 requirement that will require careful thought and implementation, not least that, as of the date of writing, no decision has been made as to how a Notified Body would issue an opinion on the device element of a medicinal product.

The overall implication of the MDR is that the device element of the medicinal product would not be treated as a fully CE-marked device but the Annex I requirements would still need to be met – as indeed was the case with the MDD. It should be noted however, that Annex I of the MDR has been expanded significantly and as such, it is likely that application for a medicinal product device element would not be dissimilar to that for application of

"With an increasing shift away from small molecule drugs toward biologics and an increased desire for patient self-administration to reduce the burden on healthcare systems, the option to combine a drug formulation with an integrated delivery device seems increasingly likely. There are some key implications of the Article 117 requirement that will require careful thought and implementation, not least that, as of the date of writing, no decision has been made as to how a Notified Body would issue an opinion on the device element of a medicinal product."

the CE-mark; with the declaration of conformity being the significant omission. This also allows for continuing to handle the product development under the MPD and pharmaceutical practices.

It is assumed that a Notified Body would not issue a CE-mark certificate, and it is probable that a Notified Body would issue some form of report to the manufacturer, detailing an opinion of the conformity of the device. This report could be included either as part of the marketing authorization application or as a separate communication to the competent authority.

The question then arises as to the format of any submission to a Notified Body and the information that would be assessed as part of that submission. For a CE mark applied to a medical device, this information would typically be presented as part of the summary technical documentation (STED) rather than in the appropriate section of the Marketing Authorization Application (MAA) as for the device element of a medicinal product. It is possible that section 3.2.R of the MAA, containing the device elements could be submitted to the Notified Body; however, it is likely that there will need to be some revision of this section to ensure it captures all of the required information. Alternatively, a new section could be created in the application to assess the Annex I requirements separately.

Clarification is also needed as to how a Notified Body would form an opinion on the device element of a medicinal product. Currently, medical devices are assessed on a risk-based principle, with the device classification determining assessment routes and additional requirements. Device elements of medicinal products are likely to automatically increase the risk classification due to the presence of the drug product. It should also be considered that even a device element that would be classed as a class I medical device – and thus subject to self-certification – would still need a Notified Body review and opinion.

Within the submission itself, it is worth considering that the system should not be simply split down the middle between the device element and drug. Whilst it is true that certain elements lend themselves to one route or the other – for example formulation versus material selection – many cannot be assessed in isolation. Certain attributes have relevance to both the drug and device elements. For example, the siliconization level in a pre-filled syringe may be impacted by the drug formulation, but is also key when considering the mechanical forces required to operate an auto-injector, especially over a claimed shelf-life. Therefore, it is important that assessment of any individual element also accounts for the interface and interaction of that element with other parts of the system. This is a critical element where the MAA and Notified Body evaluation may differ in their overall assessment of risk.

AFTER APPROVAL?

Post-market surveillance (PMS) is one of the most significant updates captured in the MDR. There is an increased requirement for manufacturers to take a more proactive approach to PMS and actively assess performance of medical devices once they are launched on the market, rather than purely relying on user feedback. Medicinal products are subject to their own PMS requirements, but it is likely that the device elements of medicinal products would have an increased requirement for PMS in line with the MDR.

Post-approval changes to a medicinal product with an integrated device element

would likely need to be captured via the medicinal product variation procedures and would be assessed by the competent authority. It is not clear at which point a Notified Body assessment would be required, although it is likely that significant changes to the device element would require Notified Body involvement. The question arises as to when changes to one element of the product cease to impact on the other element(s) and thus when the requirement for Notified Body opinion would be triggered.

Existing marketed products pose an interesting question under Article 117. The MDR has been very clear that "grandfathering" of existing products is no longer permitted, and new certificates need to be issued for all medical devices in class 2 or higher. The case is not so clear cut for medicinal products and their integrated device elements, as such products fall under the medicinal products system. It is possible that implementation of the MDR would not apply to products previously assessed by a competent authority as part of a MAA. If this were not the case and Article 117 changes were applicable, significant remediation activities would be needed across industry. As with much of the regulatory situation at the moment, the position is currently unclear and may not become so until it is too late to change without significant resource and cost expenditure.

WHAT NEXT?

One of the obvious major impacts of the introduction of Article 117 is the need for pharmaceutical companies to involve a Notified Body. This has implications given the other changes in the medical device world in Europe. With the implementation of the MDR and the potential loss of UK notified bodies due to Brexit, notified bodies are currently limited on resource and may not be taking on new clients for the foreseeable future.

Selection of a suitable Notified Body also involves the capability of that Notified Body to assess a specific product type with an increased requirement for that Notified Body to demonstrate the relevant expertise in a product type. The additional complication is that currently, designation of notified bodies under the MDR has not been completed, so it is unclear as to which product codes notified bodies may assess against, which a Notified Body has chosen not to apply to assess, or which are relevant for medicinal products with integrated device elements.

SUMMARY

In the regulatory arena, regulations and guidelines are always open to interpretation, and many regulatory professionals have been known to utter the words "it depends" when called upon to clarify. This seems unlikely to change with the implementation of the Medical Device Regulation, especially with regard to Article 117. What is clear however, is that with so much detail currently undefined and likely to remain so until the date of application in May 2020, impact assessments need to be performed, and companies need to have open discussions with notified bodies, if not already started, to ensure that appropriate support is available when needed. The time, effort, and skills required to implement the coming changes should not be underestimated and, as ever, the clock is ticking. ◆

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3. Medical Device Directive. Directive 93/42/EEC
4. In Vitro Diagnostic Directive. Directive 98/79/EC
5. Active Implantable Device Directive. Directive 90/385/EEC

BIOGRAPHY

Louise Place is Regulatory Lead at Cambridge Design Partnership, a full-service product development consultancy based in Cambridge, UK, and Palo Alto, TX. Originally training as a pharmaceutical scientist at Nottingham University, UK, she has more than 10 years of experience in medical device and combination product development with a particular focus on device technical management and regulatory strategy for FDA and EU submissions.

TOPICAL DELIVERY

Novel Approaches to Topical Antibiotics Promise Innovation in the Treatment of Acne & Rosacea

By: G. Scott Herron, MD, PhD

INTRODUCTION

As antibiotic resistance becomes frighteningly routine, dermatologists worried about their heavy reliance on these drugs are on a quest to find new ways to treat common skin conditions like acne and rosacea, which affect up to 66 million Americans (50 million and 16 million, respectively).[1]

The medical community is expressing enthusiasm for some promising new therapeutic products in clinical trials. These products – using a novel formulation of minocycline – have the potential to be the first real advances in antibiotic acne treatment in nearly 40 years.

Innovation is critically important. Dermatologists represent 1% or less of the US physician population, yet they order nearly 5% of antibiotic prescriptions.[2] Between 2003 and 2013, they prescribed antibiotics up to 9 million times annually – representing at least 20% of all their prescriptions. Up to two-thirds of these antibiotic prescriptions were for the treatment of acne vulgaris.[3-6]

The most effective antibiotics – and the most commonly prescribed – are in the tetracycline class. Unfortunately, the most effective formulations of tetracycline-class antibiotics like doxycycline and minocycline are only available as orals, which cause greater concerns about antibiotic resistance. These oral formulations flood the bloodstream with drugs in order to reach the microbes in the skin being targeted for treatment. This increases the likelihood that bacteria will become resistant to the medicine and significantly increases the risk of antibiotic resistance in dermatology patients.

THE ANTIBIOTIC RESISTANCE PROBLEM IS REAL

Studies show dermatologists have few satisfactory alternatives to oral antibiotics.[7] For example, minocycline, which is a commonly prescribed oral antibiotic and seems to have the least potential for resistance of the tetracycline class, is not commercially available in topical form.[8,9] Meanwhile, many of the antibiotics that are available as topical products, such as clindamycin and erythromycin, have surprisingly high resistance rates, and therefore are marginal in efficacy.[7] As Table 1 shows, the antibiotic resistance problem is enormous.

TABLE 1

Country	*P. acnes* Resistance Rate (%)		
	Clindamycin	Erythromycin	Azithromycin
Spain[10]	91	91	--
India[9]	90	98	100
United States[11]	100	100	--

This is why dermatologists have been forced to embrace a standard of care using combination therapies that alternate the use of oral antibiotics and topical products like benzoyl peroxide or retinoids. These combinations offer the best-available treatment and are currently recommended by the American Academy of Dermatology.[12]

But these combination therapies have their own shortcomings. For example, the antimicrobial benzoyl peroxide is associated with adverse effects, such as stinging, burning, itchiness, dry skin, irritation, and bleaching of dark clothing. This poses two problems. First, side effects often deter adherence. Second, patients frequently do not follow physician instructions about using

benzoyl peroxide along with the topical antibiotic and use the antibiotic alone.[13]

NEEDED: ALTERNATIVE WAYS TO DELIVER ANTIBIOTICS

Dermatologists and their patients need a better way to deliver antibiotics effectively without contributing to the resistance problem.[14] An ideal solution might be a new topical antibiotic formulation that could theoretically deliver effective therapy in a more targeted way with a lower dosage of antibiotic, thereby reducing the risk of antibiotic resistance associated with oral formulations.

That better solution may be on the horizon. Two companies have developed topical formulations of one of the most effective tetracycline-family antibiotics: minocycline. BioPharmX, Inc. of California and Foamix Pharmaceuticals of Israel attack the problem differently but both have products in the clinical research stage.

Minocycline, a second-generation tetracycline, is appealing because it demonstrates the lowest resistance rates of all the tetracycline class of antibiotics.[6,7,15] It is particularly effective in managing several different inflammatory skin diseases, and its oral formulation is one of the most prescribed antibiotics for acne. While oral minocycline was long perceived to be more effective in the treatment of acne than other antibiotics, its use has decreased somewhat over concerns about its safety, including the risk of systemic side effects, such as headache, dizziness, nausea, hyperpigmentation of skin and teeth, autoimmune hepatitis, systemic lupus erythematosus, and ANCA vasculitis.[16]

A topical formulation of minocycline should remove these risks by significantly reducing or even eliminating the systemic exposure through precise delivery to the layer of skin where treatment is needed and the reliance on dosages that are just a fraction of the standard oral dosage.

Several companies have unsuccessfully attempted to develop commercial topical or transdermal delivery systems for minocycline for the US market. For years, researchers have been unable to stabilize minocycline in a delivery system that can penetrate the stratum corneum, the outer layer of the epidermis.

TWO APPROACHES TO A TOPICAL MINOCYCLINE

BioPharmX has solubilized minocycline with HyantX™, an anhydrous hydrophilic topical gel system that research shows delivers minocycline into the pilosebaceous unit. Foamix delivers a suspension of minocycline using a foam formulation that research shows allows antibiotic penetration. Both formulations are in clinical trials to assess their use in treatment of certain dermatological skin conditions, including acne and rosacea.

Both products hold out the promise of delivering effective levels of minocycline. However, the differences between the two companies' delivery systems may affect each product's utility in dermatological care.

The BioPharmX gel delivery system promises to be a cosmetically elegant solution. The gel fully solubilizes minocycline and leaves no trace of the antibiotic on the skin. It also leaves no oily residue on the skin that may discourage patient compliance. The BioPharmX BPX-01 topical minocycline gel formulation for acne also evaporates, which increases the surface concentration gradient to enhance delivery of the API into the skin and can soothe and cool the skin. Clinical research on BPX-01, a 2% minocycline concentration, found the medication was well tolerated with a good safety profile and was virtually undetectable in blood plasma.[17] As a result, no systemic side effects are anticipated. Subjects in the clinical trial also demonstrated rapid improvement and better outcomes than vehicle control in the treatment of moderate-to-severe non-nodular inflammatory acne vulgaris.[18] This treatment may provide an effective new option with a favorable safety profile and potential for high patient compliance.

It is worth highlighting that the HyantX delivery system contains a number of excipients, including ethanol, which is a versatile solvent, miscible with both

water and lipids, and also penetrates the skin.[19,20] This helps deliver minocycline into the epidermis and pilosebaceous unit. Ethanol is naturally bactericidal, non-bleaching of skin and clothing, and is designed to be non-irritating in the BioPharmX formulation. In sufficient concentration, ethanol has a therapeutic effect in the treatment of P. acnes (BPX-01 vehicle contains ethanol levels above MIC/MBC).

The Foamix foam suspends minocycline and leaves residue on the skin that may irritate the skin and stain clothes and bedding.[21] While researchers detected minocycline in the pilosebaceous unit, including the hair follicle and the sebaceous gland, it is not clear whether the lipid-based foams will clog pores, something that may be worrisome for acne patients and their clinicians.

It is interesting to note that, based on clinical trials, the two companies use different concentrations of minocycline in their products. BioPharmX uses 2% solubilized minocycline in BPX-01 gel, while Foamix uses double the concentration – or 4% minocycline. The higher Foamix concentration may be needed for a few reasons. In its formulation, the minocycline is not dissolved, it is suspended in the foam. This may make it more difficult for the minocycline to penetrate into the pilosebaceous unit, against the flow of sebum. Accordingly, the foam vehicle remains on the skin to help penetration, but with more drug, which may irritate the skin and clog pores.

CLINICAL RESULTS ARE PROMISING

Both BioPharmX and Foamix have reported clinical research data suggesting their products work.

A novel Fluorescence Lifetime Imaging Microscopy (FLIM) analysis of the BioPharmX BPX-01 topical gel penetration into the skin demonstrated detectable fluorescence of minocycline following a single daily application after a 24-hour incubation period. Minocycline was detected at 2.5 mg/cm2 and was found in the epidermis, infundibulum, hair follicle, and sebaceous glands.[22] This analysis is noteworthy because it represents the first time FLIM was used to determine minocycline penetration in the skin, and it is the most accurate and precise measurement method of such penetration undertaken to date with a single daily dose.

In a randomized and vehicle controlled clinical trial, the BioPharmX formulation showed rapid improvement in clinical onset. There was a 25% reduction in lesions at week 2 of a Phase 2b clinical trial, a 43.3% reduction at week 4, and a 58.5% reduction at week 12. Compared to oral formulations of minocycline, such as Solodyn®, BioPharmX was able to achieve results comparable to 12-week efficacy of oral minocycline in only 4 weeks.[17] The treatment was found to be generally safe and well tolerated in the clinical study setting thus far. No serious treatment-related adverse effects were reported. Neither were photosensitivity or post-inflammation hyperpigmentation, nor adverse events of staining and/or skin discoloration. A participant survey conducted as part of the trial also found that BPX-01 was considered by patients as a positive experience, with most subjects saying they would consider using the product again.[23]

An analysis of the Foamix FMX101 minocycline foam product showed that most of the antibiotic remained unabsorbed as residue on the skin surface. Nonetheless, appreciable amounts of minocycline did accumulate in the skin following 24 hours of drug treatment. The total mean amount of minocycline in the skin was 108.90µg (≡61.52 µg/cm^2) for the 4% formulation. The stratum corneum, including its deeper layers, contained 105.41±24.98 µg (≡ 59.55 µg/cm^2) for the 4% formulation.[21]

As with the BioPharmX product, the Foamix solution resulted in significant improvement to patients. The company's two trials reported reductions in the number of inflammatory lesions of 43.93% and 42.94% after 12 weeks.[24] However, Foamix failed one of its endpoints in its

Phase 3 studies, likely due to insufficient patient numbers, and extended the trial to add a third study.

HOW MUCH UPTAKE IS ENOUGH?

It has been shown that the minimum inhibitory concentration (MIC) for a typical strain of P. acnes is approximately 30 ng/mL for minocycline. As a result, the dosage applied on the skin in both BPX-01 2% and FMX101 4% are above the concentration required to address surface proliferation of these bacteria.

Further, because the HyantX delivery system contains ethanol, which is bactericidal, it could potentially help address the concerns of development of bacterial resistance against minocycline, similarly as benzoyl peroxide does for clindamycin in combined topical formulations.

Additionally, minocycline in BPX-01 is fully solubilized, as opposed to being in suspension in FMX101. This may have an impact on bioavailability of minocycline for each formulation.

CONCLUSION

Both the BioPharmX and Foamix products offer promise to a dermatologic community that is eager to have effective new therapies that may reduce the risk of systemic antibiotic resistance. Despite ongoing efforts to identify alternatives to antibiotics for the treatment of conditions like acne and rosacea, the substitutes have not been ideal. Research continues to find alternatives.

One thing is certain - the dermatologic community is anxiously awaiting a topical antibiotic such as minocycline.

Finding a way to deliver an effective topical formulation of minocycline – which has the lowest resistance rate among the tetracycline class of antibiotics – would address dermatologists' needs for delivering effective care while limiting systemic exposure to antibiotics in patients.

We look forward to the results of both companies' ongoing research in hopes that their products are found to be effective and safe enough for commercialization.◆

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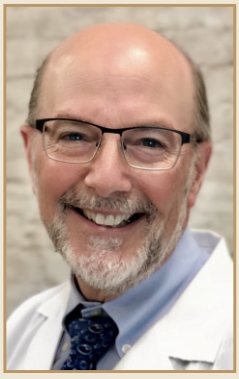
BIOGRAPHY



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CLINICAL TRIALS

Spotlight on Quality in Study Startup: Automated Workflows Encourage Upfront Planning & Downstream Improvements in the eTMF

By: Elvin Thalund, MS, and Craig Morgan

INTRODUCTION

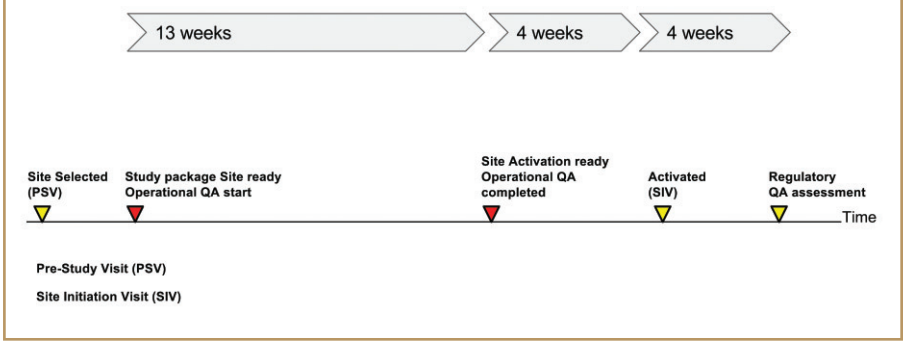
There is a dazzling array of quality initiatives within the clinical trials sector all looking to move the needle from paper-based methods or single-point solutions to a more integrated, non-siloed approach to study conduct. These efforts (Table 1) may be rooted, at least somewhat, in work started nearly 20 years ago when the Institute of Medicine published To Err is Human, a call-to-action to improve safety in our healthcare system by linking it to greater quality.[1] That seminal work was followed by various reports recognizing the urgent need to transform the clinical trials enterprise by focusing more intently on quality.[2,3]

Emphasis on quality is everywhere, but in particular, the study startup portion of clinical trials is a particular hotspot, as it is pivotal to improving study conduct overall. Specifically, as a complex multi-step process, it is renowned for bottlenecks that cause a seemingly intractable 8-month timeframe for moving from pre-visit through site initiation.[4] Improving this bleak performance is important because study startup generates more than 40% of the artifacts that eventually flow into the trial master file (TMF).[5]

With unrelenting pressures to rein in budgets and cycle times, stakeholders are turning to quality as a solution, starting with building it into study startup and bringing change to the entrenched silos that stall clinical trial operations. The process starts by recognizing that many elements of clinical trial execution are rolled out during study startup, making proactive planning a priority. Without this critical step, study conduct can be delayed, siloed efforts continue, and documents eventually released to the TMF or eTMF may be missing or incomplete. Fortunately, workflow-based study startup tools are available that facilitate a proactive planning process for stakeholders seeking to improve quality by determining which documents are needed and in which format. This forward-thinking approach supports audit-readiness and greater likelihood of passing regulatory audits.

As part of proactive planning, the clinical operations team is responsible for identifying the necessary workflows, such as contract and budget agreements, and documents for the institutional review board. Once these are established, and study conduct begins, downstream functions are often handled in a tightly guarded siloed atmosphere, with each department generating its own standard operating procedures and budgets. Typical of this isolated approach is a lack of institutional knowledge of what the next department needs to fulfill its regulatory obligations and conform to performance metrics. For example, the clinical operations team may not know which documents are needed in the TMF and may be unfamiliar with the accepted format and relevant metadata. Unfortunately, these deficiencies are not detected until much later, which can harm study quality, disrupt timelines, and increase cost of operations. With a workflow-based system, however, these challenges are hammered out upfront, so problems caused by not knowing the needs of the next department are eliminated.

FIGURE 1



QUALITY STARTS EARLY

Quality is fundamental to clinical trials, but with cycle times stagnating for two decades, there is an intense focus on this subject.[6] In a 2008 presentation by the Clinical Trials Transformation Initiative (CTTI), quality was defined as the ability to effectively and efficiently answer the key performance question(s) (KPQs) about the benefits and risks of a medical product or procedure while ensuring protection of human subjects.[7] In answering KPQs, stakeholders are looking to industry-based metrics to measure performance. For example, one performance metric determines compliance by suggesting that regulatory quality assurance should occur 4 weeks after site activation, one of the final steps of study startup.[8] But, with this timeframe, problems such as missing or incomplete documents may go unnoticed until this late date, when the study is already well underway.

A better strategy is to employ upfront workflows designed to prevent or mitigate problems associated with document completion. As shown in Figure 1, the 4-week post-activation quality assurance timeframe plus the 17 weeks needed for development of the study package through to study activation yields a lengthy 21 weeks. Instead, if the workflow process starts from the beginning of the clinical trial — with developing the study package — artifacts and documents are developed 17 weeks earlier, well before study activation, problem detection can occur months sooner.[9] This is a major improvement that helps ensure the quality of TMF artifacts and associated metadata downstream and enables audit readiness.

To better educate stakeholders about the critical importance of early commitment to quality in clinical trials, the Metrics Champion Consortium (MCC) has launched the MCC Study Quality Trailblazer Team.[10] This team seeks to help its members set an example for the rest of the industry by demonstrating that investing time and resources upfront can yield higher quality clinical study performance at a lower cost than attempting to fix quality issues later on, after the study is underway. The Trailblazers aim to achieve this by implementing changes that:

- Do a better job of identifying and reducing risks before the start of a study
- Produce high-quality protocols
- Oversee risks during the study

They have also released a white paper, which uses data from the Tufts Center for the Study of Drug Development (CSDD) to document that study quality is actually declining despite major advancements in technology over the past 20 years, often due to issues that are preventable.[11]

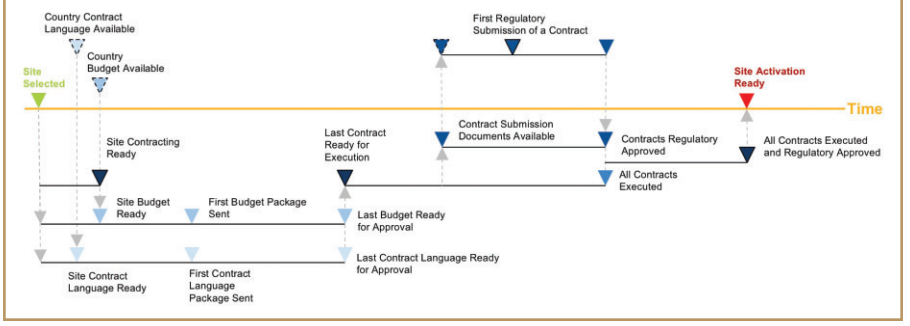
Reversing this trend means building in quality from the start, and significantly, this approach aligns with regulatory initiatives to upgrade study quality. One of the most widely anticipated was the November 2016 release of the first new Good Clinical Practice guideline (GCP) in 20 years.[12] Put forth by the International Conference on Harmonisation (ICH), the guideline, known as ICH-GCP E6(R2), includes Section 5.0, which defines Quality Management. It states that the sponsor should implement a system to manage quality throughout all stages of the trial process. This section addresses topics such as critical process and data identification fol-

TABLE 1

Some Initiatives Focused on Quality Improvement (alphabetical)

- Alliance for Clinical Research Excellence & Safety (ACRES)
- Avoca Quality Consortium
- Clinical Trials Transformation Initiative (CTTI) (Includes Quality by Design)
- Metrics Champion Consortium
- TransCelerate BioPharma
- Trial Master File Reference Model - Quality Sub-Group

FIGURE 2



lowed by sub-sections dedicated to risk factors, namely risk identification, risk evaluation, and more. Furthermore, the sponsor is to ensure that operational documents such as the protocol, case report forms, and others are to be concise and consistent, and all aspects of the trial are operationally feasible.

The ICH-GCP E6(R2) guideline follows on the heels of regulatory documents released by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in 2013, citing that risk-based quality management should start prospectively, meaning early on, as clinical trials are preparing for launch (Table 2).[13,14] The new ICH-GCP guideline builds on this foundation.

BREAKING DOWN SILOS

In the ongoing discussion of factors contributing to poor quality in clinical trials, the EMA Reflection Paper cites fragmentation of all sorts — lack of clear distribution of roles among players, piecemeal implementation of technology, unconnected standardized solutions — as causes of quality issues. This insight reflects the siloed approach that has long typified clinical trial operations and continues to do so. It is often casually referred to as the "throw it over the wall" mentality, meaning that once a specific department has completed its work, it is tossed over the wall to the next department, with little understanding of what is needed downstream.[15]

This awkward management style is one of the root causes of problems with the TMF and eTMF. Specifically, information about the standardized taxonomy and metadata provided in the TMF Reference Model is not shared with clinical operations team members, so they are often unaware of the documents needed or the required format for release into the TMF. Later on, this is problematic for the regulatory group tasked with mapping documents to the TMF, as well as indexing the metadata, as startup generates nearly half of the TMF artifacts.[5]

There is a growing body of literature detailing how breaking down silos is pivotal to better study execution. A recent article by Melissa Fassbender notes clinical trial technology has evolved to the point that forward-thinking companies will soon distinguish themselves by moving away from vertical silos and embracing "thinking horizontally." This refers to using automation and workflows to integrate operational data across all functions.[16] And using this approach, it will be easier to extract meaningful insights from those data and answer KPQs.

Similarly, other articles are promoting the importance of eliminating silos in favor of a cross-functional, horizontal method for critical operations such as contracts and budgeting, and governance.[17,18] Strategy &, PwC's strategy consulting group, published a lengthy report on the cross-functional team method as key to revamping the siloed business model that is all too common in the pharmaceutical sector.[19] They note that interdependent functions should be brought together through critical teams and through the use of technology to better navigate today's complicated regulatory maze. And while cross-functional teams are not a panacea, they are an important first step in moving away from the traditional "over-the-wall" mentality.

QUALITY THROUGH WORKFLOWS

Optimizing study conduct starts with embracing a workflow-based approach to defining the documents needed for the multi-step study startup process. This method boosts the quality of study conduct by preparing documents that are accurate, complete, and conform to the eTMF format established by a sponsor's or contract research organization's (CRO) regulatory team, enhancing audit readiness.

Study startup workflow-based solutions facilitate quality efforts by integrating data flow from several eClinical solutions, such as electronic data capture, the clinical trial management system and eTMF, ensuring an end-to-end continuum that allows properly formatted documents and structured artifacts to flow into the eTMF.

With the help of workflows, any and all documents eventually needed for the TMF or eTMF can be defined. This is a major advantage because typically there are more than 400 draft and supporting artifacts that can be structured using a workflow-based tool, resulting in a final set

TABLE 2

Regulatory Agencies Suggest Building in Quality From the Beginning

European Medicines Agency

The identification of priorities and potential risks should commence at a very early stage in the preparation of a trial, as part of the basic design process. The concerns with trial and protocol design, design of data collection tools/instruments, the design of the monitoring and data management strategies and plans…and the design of record keeping for the study should be addressed… implementing a quality by design approach.

Food and Drug Administration

Sponsors should prospectively identify critical data and processes, then perform a risk assessment to identify and understand the risks that could affect the collection of critical data or the performance of critical processes.

Source: EMA Reflection Paper; FDA Guidance 2013

of approximated 60 artifacts that will ultimately be released into the eTMF. One example is the completed clinical trial agreement, which is composed of numerous sub-artifacts, as shown in Figure 2.

FOR QUALITY, PLAN & BREAK DOWN SILOS

Across the industry, proactive planning for improved clinical trial quality is in early stages, but with the availability of workflow-based tools starting from study startup, process changes are taking root. These changes look to be transformational as the documents, artifacts, and associated metadata needed for the eTMF can be planned upfront. Using this approach, entrenched silos will no longer be obstacles to the downstream regulatory team receiving accurate and correctly formatted documents from previous groups in what has often been a long and inefficient chain of study execution. In its place is a more efficient process that streamlines data collection in the format needed by the regulatory group to map the information in the eTMF.

By implementing this approach, stakeholders enjoy the benefits of being audit ready, information will be more easily retrievable, and there is a greater likelihood of adherence to cycle times and budgets. And critically, issues will be identified early on, rather than waiting until they reach the eTMF. As the industry turns its attention to quality improvement, these positive outcomes will encourage widespread acceptance of this strategy.◆

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BIOGRAPHIES

Elvin Thalund is the Director, Industry Strategy at Oracle Health Sciences. He is a recognized industry expert in clinical trials, having over 20 years of experience working as a Clinical Business Analyst Consultant at major pharmaceutical companies, including Hoffmann-La Roche and Johnson & Johnson. He is the co-chair on the TMF Reference Model Exchange Mechanism and earned his Master of Science in Industrial Engineering from Aalborg Universitet.

Craig Morgan is the Head of Marketing, Study Start Up at Oracle Health Sciences. He is a technology and life sciences management professional with more than 15 years of experience in the application of informatics and bioinformatics to drug discovery. His passion is transforming study management and trial execution processes, which are supported by facilitating systems, to allow sponsors, CROs, and sites to reduce cycle times and improve collaboration and oversight in clinical trials.

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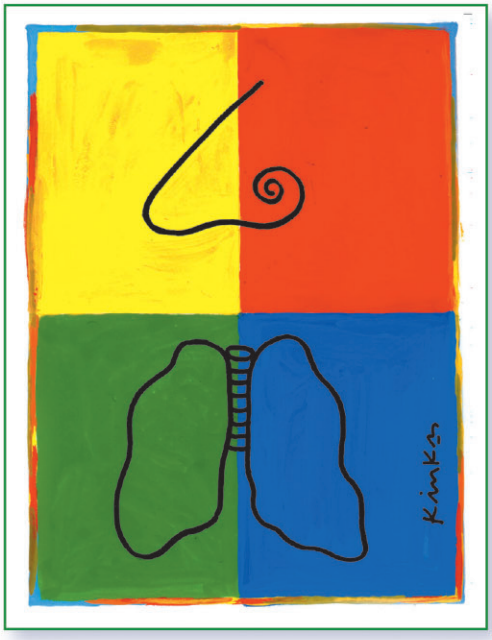

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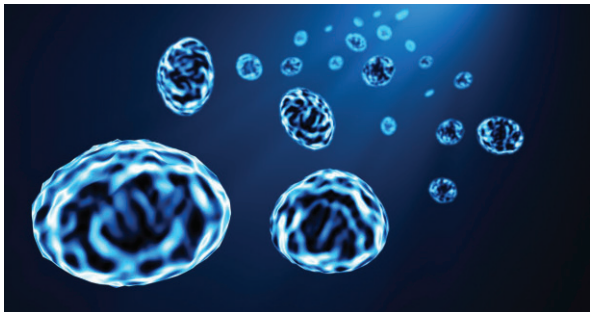

Ascendia Pharmaceuticals is a contract development and manufacturing (CDMO) company offering services for formulation development of poorly soluble drugs and other challenging development programs. Our formulation options include nanoemulsions, amorphous solid dispersions, nanoparticles, liposomes, and oral controlled release. These technologies are suitable for oral, topical, or injectable dosage forms. NanoSol is our technology for production of nanoparticle formulations. Ascendia has the capability to make nanoparticles from native drug crystals using ball milling, or lipid-based nanoparticle composites for lipophilic drugs. When the nanoparticle is delivered to the body there is greater surface area for dissolution, and by using enhancers in the formulation higher bioavailability can be more readily achieved. Ascendia can optimize nanoparticle formulations and produce clinical trial materials for first-in- man studies. For more information, contact Ascendia at (732) 640-0058 or visit **www.ascendiapharma.com.**

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Technology & Services Showcase

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Backed by over 85 years of experience in parenterals, **Baxter's BioPharma Solutions (BPS)** business collaborates with pharmaceutical companies to support commercialization objectives for their molecules. BPS is a premier CMO with a focus on injectable pharmaceutical manufacturing designed to meet complex and traditional sterile manufacturing challenges with confidence of delivery, service, and integrity. BPS can support your pharmaceutical needs with a broad portfolio of sterile fill/finish production capabilities, and our reputation is built on the high-quality products we manufacture for our clients in a cGMP environment. Our delivery systems include: prefilled syringes, liquid/lyophilized vials, diluents for reconstitution, cartridges, powder-filled vials, and sterile crystallization. For more information, visit Baxter BioPharma Solutions at **www.baxterbiopharmasolutions.com.**

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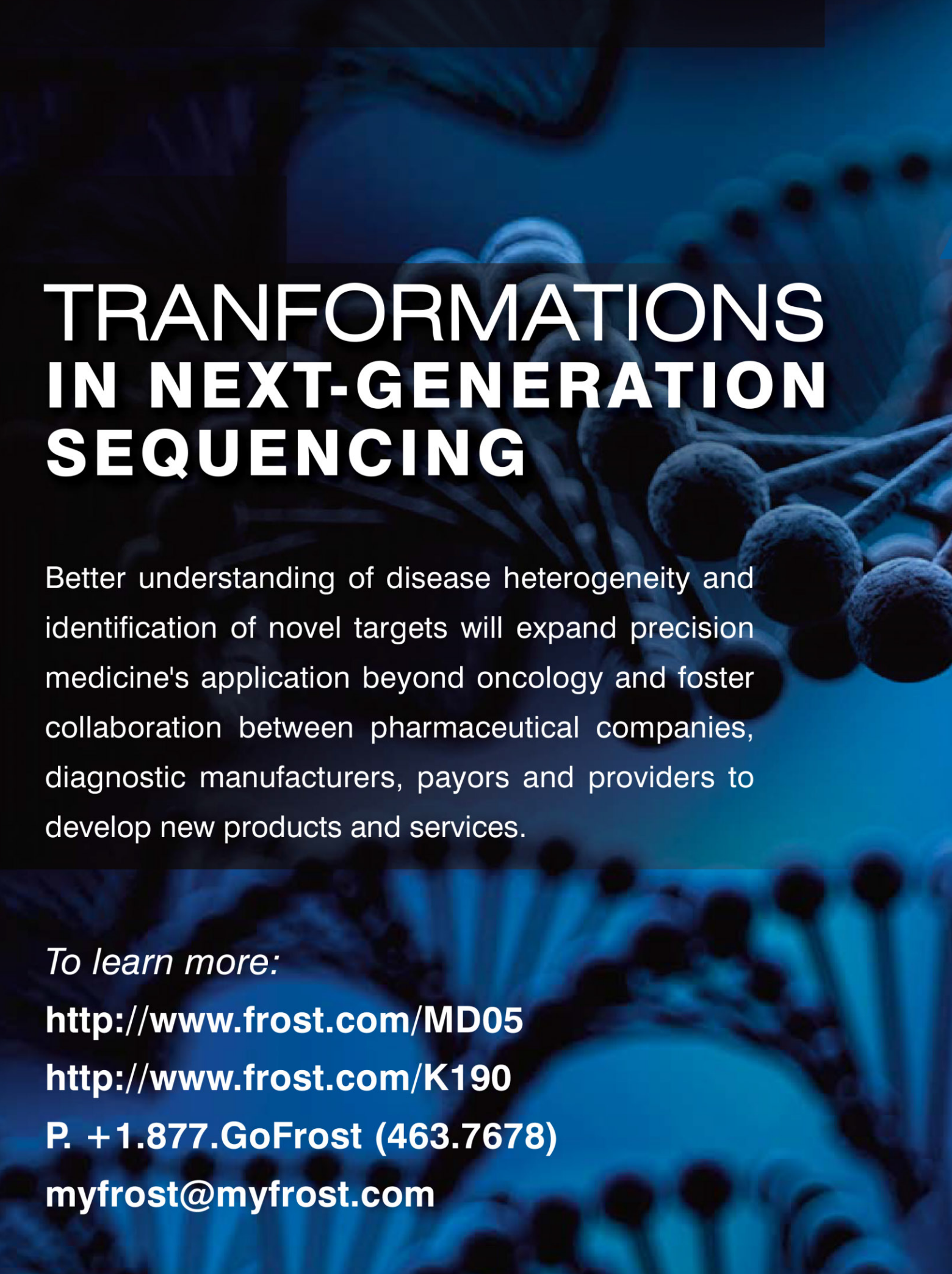
Captisol is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Captisol was invented and initially developed by scientists in the laboratories of Dr. Valentino Stella at the University of Kansas' Higuchi Biosciences Center for specific use in drug development and formulation. This unique technology has enabled 11 FDA-approved products, including Onyx Pharmaceuticals' Kyprolis®, Baxter International's Nexterone®, and Merck's NOXAFIL IV. There are more than 30 Captisol-enabled products currently in clinical development. For more information, visit Captisol at **www.captisol.com.**

Bioavailability & Development Toolkit

With 85 years' experience serving the pharmaceutical industry, **Catalent** is the leading global provider of advanced drug delivery technologies and development solutions for drugs, biologics, and consumer health products. These solutions include analytical, pre-formulation and formulation technologies, and expertise, and Catalent also offers its partners the broadest toolkit of bioavailability-enhancing technologies for early phase drug development. Its experience helps introduce more than 150 new products to market every year. Catalent's multi-award-winning OptiForm® Solution Suite platform can assist in the development of innovative dose forms that can improve a drug's clinical efficacy and commercial success. OptiForm Solution Suite is fast, flexible, and fact-based, combining the broadest selection of enabling technologies to ensure that right decisions are made at each stage of development. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com.**



TRANFORMATIONS IN NEXT-GENERATION SEQUENCING

Better understanding of disease heterogeneity and identification of novel targets will expand precision medicine's application beyond oncology and foster collaboration between pharmaceutical companies, diagnostic manufacturers, payors and providers to develop new products and services.

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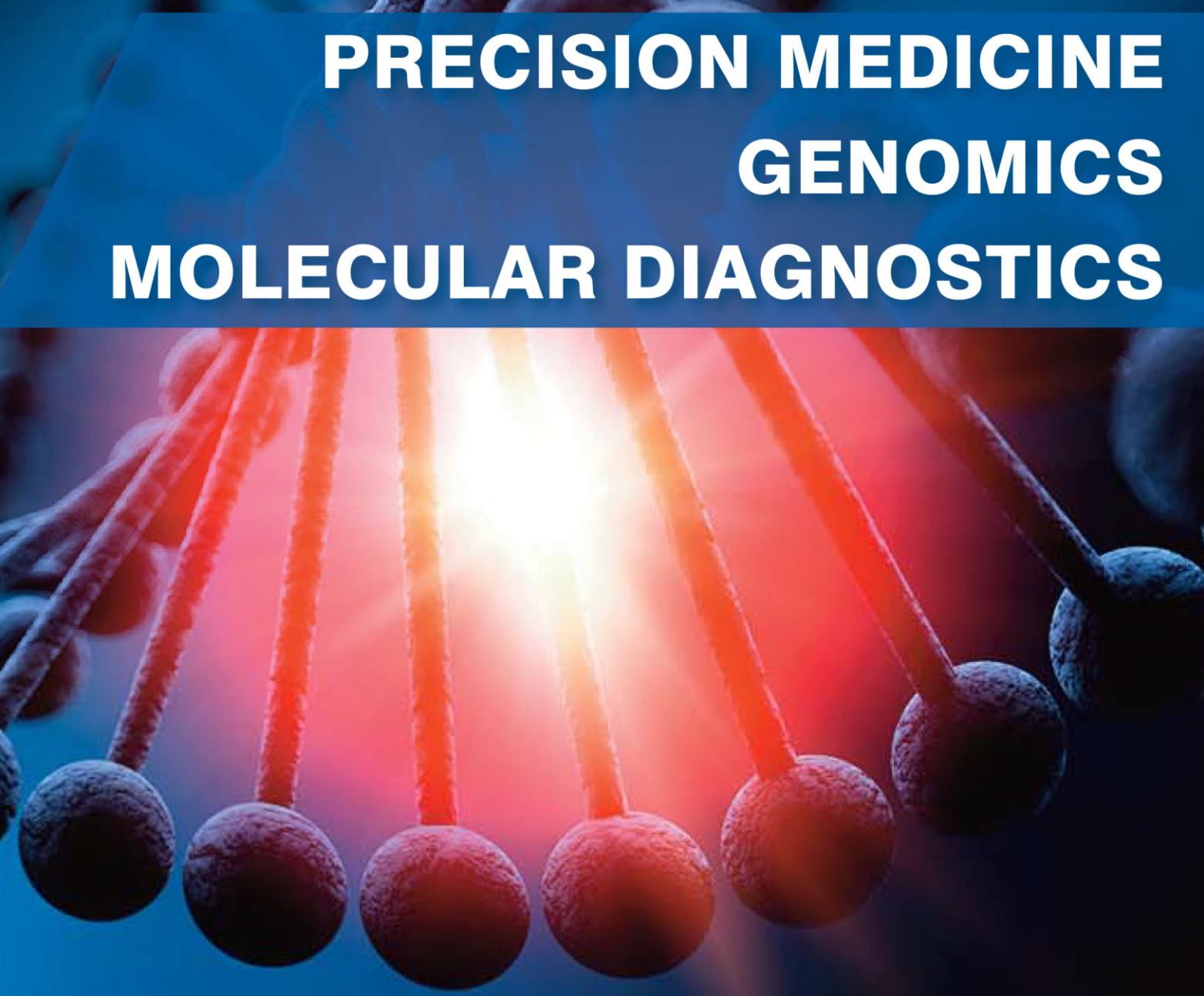

The Frost & Sullivan Global Life Sciences Program helps you identify stakeholder dynamics as the healthcare system transitions from acute care into integrated care.

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

Technology & Services Showcase

Differentiated Injectable Delivery

Credence MedSystems is a medical technology company focused on delivering medications safely for the benefit of our patients, caregivers and partners. The Companion Safety Syringe System was born from Credence's core philosophy of *Innovation Without Change*. By providing passive safety and reuse prevention while using existing primary package components, the Companion offers best-in-class drug delivery with a vastly simplified path to market for our biotech and pharmaceutical partners. The Companion is available in luer needle, staked needle and dual chamber reconstitution configurations. In all cases, the user performs the injection, receives end-of-dose cues and then the needle automatically retracts into the syringe, which is then disabled. For more information, contact Credence MedSystems at 1-844-CMEDSYS, email info@credencemed.com, or visit **www.CredenceMed.com**.

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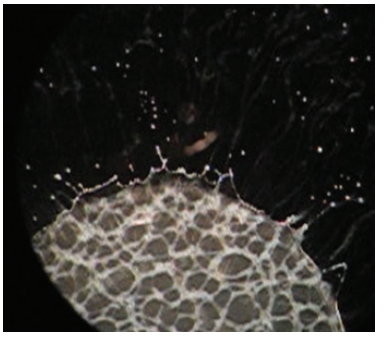
Self-Emulsifying Delivery



Gattefossé self-emulsifying drug delivery systems (SEDDS) are a simple and efficient solution for the delivery of poorly soluble compounds, and as of late for oral peptide delivery. Scientists have successfully developed SEDDS for delivery of Leuprorelin, Desmopressin, and Insulin, which has a MW of 5.8 KDa. This is made possible by hydrophobic ion-pairing of the peptide molecules and subsequently cloaking them with SEDDS formulations using Gattefossé excipients. SEDDS solubilize the peptides in the digestive tract while protecting them from enzyme degradation and glutathione reduction. Suitable excipients for effective peptide delivery include Labrasol® ALF, Gelucire® 44/14, Labrafil® M 2125 CS, and Peceol™. Solid SEDDS are also possible using processes such as granulation and hot melt extrusion. For more information, visit Gattefossé at **https://bit.ly/2xaa5BU.**

Technology & Services Showcase

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