Drug Development & Delivery

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Alternative Modified-Release Strategies

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

Ed Trappler
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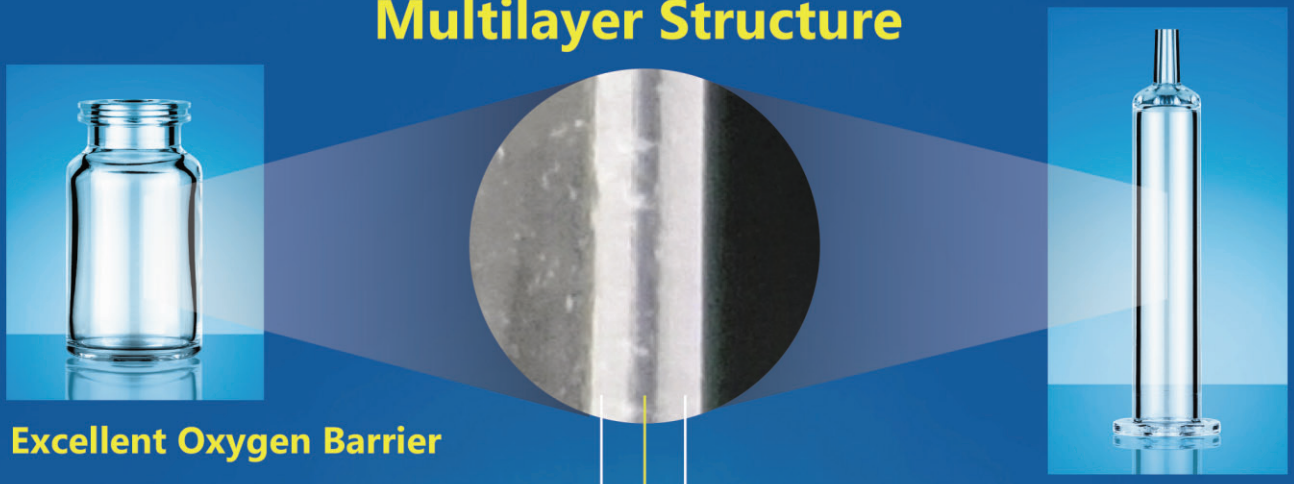

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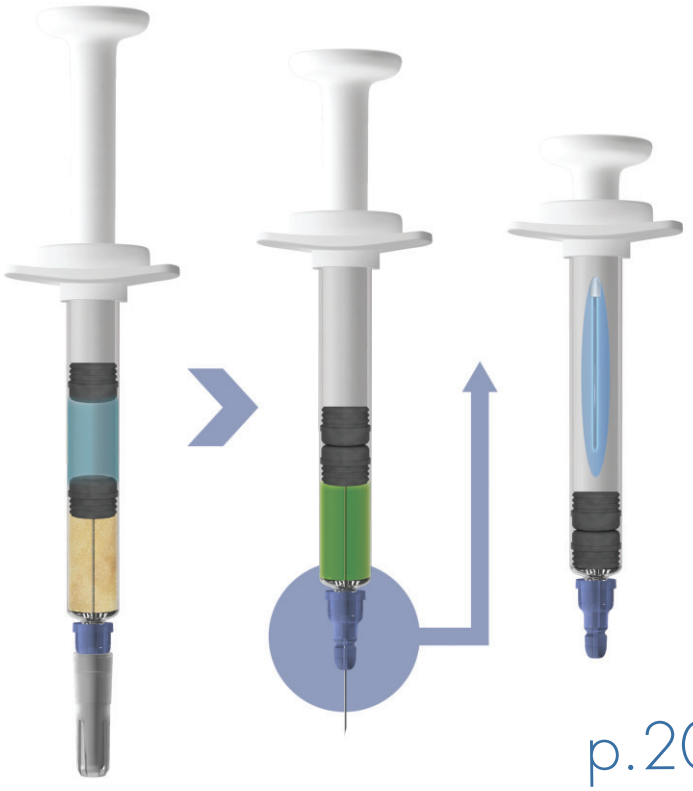
Combination Product Development

"The dual-chamber reconstitution system is a prime example of a combination product that can meet the evolving industry and patient needs. The challenge is that such combination products will require clinical, device, formulation, and process innovation as well as collaboration within the supply chain."



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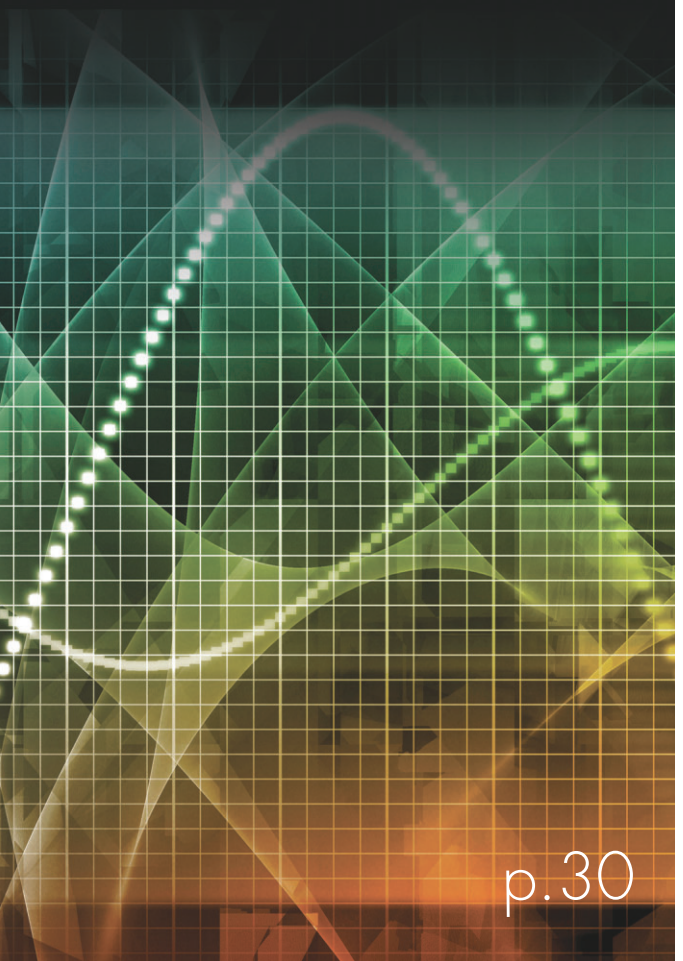
"Developing MR formulations that fit a target PK profile is far from simple, with many potential delivery technologies to select from and much uncertainty regarding performance in a physiological system. Use of a DS concept saves time and removes uncertainty surrounding achieving the clinical performance of a formulation."



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Dance Biopharm Presents Phase 2 Clinical Data Highlighting Rapid Effects of Inhaled Human Insulin

Dance Biopharm Holdings, Inc., recently presented data from its Phase 2 clinical study of Dance 501, a novel gentle mist formulation of human insulin administered with its smart inhaler, in patients with type 2 diabetes (T2D). The data were presented at the 55th Annual Meeting of the European Association for the Study of Diabetes on September 19, 2019, in Barcelona, Spain. Study results showed Dance 501 inhaled human insulin (INH) had comparable glucodynamic properties to injected insulin lispro (LIS), but delivered a faster onset of action.

"These encouraging study results demonstrate the potential of Dance 501 INH to offer a clinically meaningful benefit over rapid-acting insulin injections for patients with type 2 diabetes, while also providing a more comfortable patient experience," said Melissa Rhodes, PhD, Chief Development Officer of Dance Biopharm. "This study also further validates our smart inhaler's ability to deliver an optimal and precise dose of inhaled therapies through the lungs. A number of diseases could benefit from the frequent pulsatile administration afforded by an inhaled delivery option, so we are exploring inhaled therapies beyond human insulin where our platform could achieve better treatment efficiency."

"Dance 501 inhaled human insulin demonstrated faster onset and greater action in the first hour of administration compared to subcutaneous insulin lispro, with good tolerability in patients with type 2 diabetes," said Eric Zijlstra, PhD, lead study author and presenter. "Not only does this allow for Dance 501 INH to be administered shortly before meals, but the ease of use could potentially motivate more patients to better comply with standard medical guidance."

The randomized, controlled clinical study evaluated the pharmacodynamic action and safety of Dance 501 inhaled human insulin in comparison to injected insulin lispro in T2D patients. The study enrolled 24 subjects with type 2 diabetes on daily insulin therapy. Each patient received three doses 12, 24 and 48 U of Dance 501 (assuming a 13% relative biopotency) and subcutaneous insulin lispro. Patients received a total of six doses, administered over six visits that occurred 3 to 17 days apart. Insulin action was measured using the automated glucose clamp method over a 10-hour period following dosing.

Key findings from the clinical trial include (1) Dance 501 showed comparable pharmacodynamic properties and more rapid onset of action compared to insulin lispro, with median differences of 6.5 to 20 min, $p<0.02$, (2) Dance 501 showed greater action in the first hour of administration to lispro at all three doses with median relative differences of 45% to 107%, $p < 0.05$, (3) Time to maximum insulin action was comparable for each dose level, and (4) No safety issues, cough or acute changes in lung function were observed with any inhalation.

Accenture Announces Collaboration With Bayer

Accenture recently announced a collaboration with Bayer to implement the Accenture INTIENT Clinical platform to help simplify and speed its drug development processes. The platform, which went live at Bayer earlier this year, brings internal and external clinical data together with Oracle cloud-based technologies into a single data management and warehousing platform, creating actionable insights to accelerate drug development and improve patient outcomes.

The Accenture INTIENT Clinical platform is part of Accenture INTIENT and builds upon Accenture's market-proven platforms for research, clinical development, pharmacovigilance and patient services. It rapidly integrates new technology, advanced analytics and applied intelligence to support the delivery of patient treatments.

Bayer has also joined the Life Sciences Cloud Coalition, which was developed to enable pre-competitive collaboration between pharmaceutical companies with the goal to more quickly and cost-effectively advance clinical development. The coalition brings together Oracle Health Sciences and R&D leaders from around the world to drive innovation and digitally enable the R&D function.

Mike Stapleton, a Managing Director in Accenture's Life Sciences practice, said "We are excited to work with Bayer to provide new insights on their clinical trials, so they can bring the important treatments they develop to patients faster and with the highest quality. The future of R&D is bright when leading organizations come together to solve for patients' greatest needs."

The INTIENT Clinical platform was developed through an alliance between Accenture and Oracle. It combines Accenture's proven implementation experience with solutions such as the Oracle Health Sciences Data Management Workbench and Oracle Life Sciences Data Hub. Together, these solutions generate high-quality, reliable data from clinical trials and reduce the time, effort, and cost needed to take drugs from development to market. The Oracle solutions are powered by Oracle Cloud Infrastructure, supported with Oracle Managed Cloud Services.

"We welcome Bayer as a new member of the Life Sciences Cloud Coalition and to the Oracle Health Sciences Data Management Workbench family. Their perspective and experience will be invaluable in the advancement of clinical development for the entire industry," said Steve Rosenberg, Senior Vice President and General Manager, Oracle Health Sciences.

Accenture is a leading global professional services company, providing a broad range of services and solutions in strategy, consulting, digital, technology, and operations. Combining unmatched experience and specialized skills across more than 40 industries and all business functions — underpinned by the world's largest delivery network — Accenture works at the intersection of business and technology to help clients improve their performance and create sustainable value for their stakeholders. With 482,000 people serving clients in more than 120 countries, Accenture drives innovation to improve the way the world works and lives. For more information, visit www.accenture.com.

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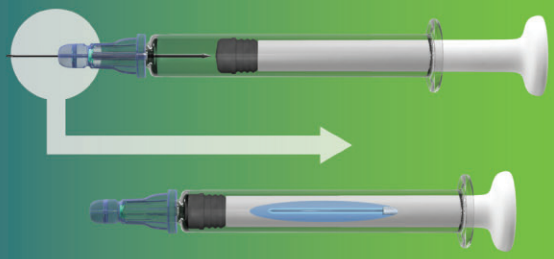

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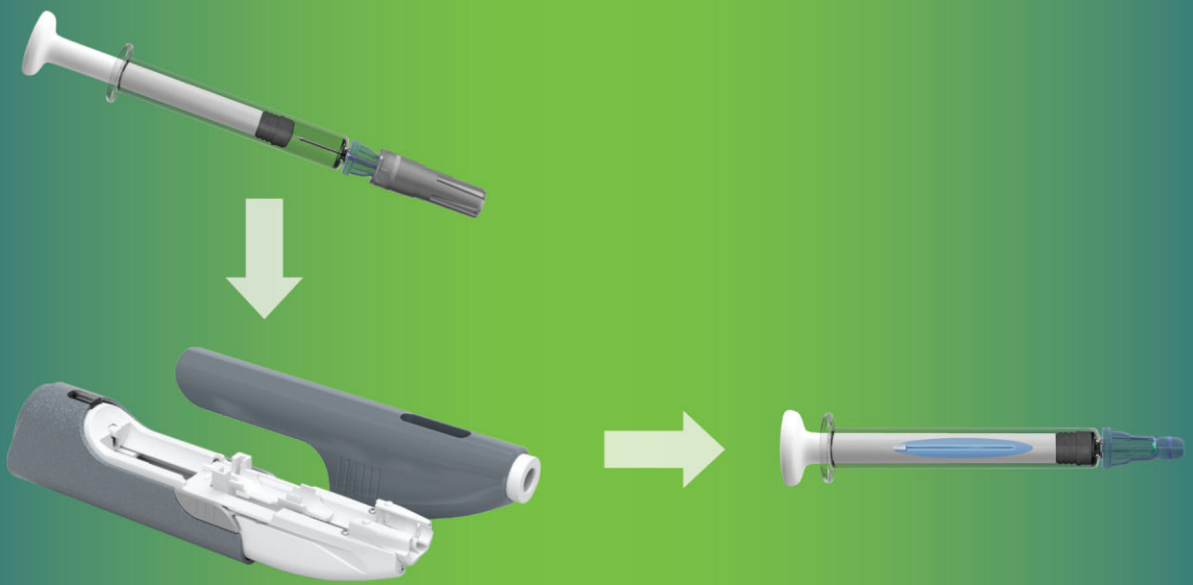

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Sanofi & Abbott Partner, Changing the Way Diabetes is Managed

Sanofi and Abbott are partnering to integrate glucose sensing and insulin delivery technologies that would help to further simplify how people with diabetes manage their condition. The two companies will take an innovative approach to connected care by developing tools that combine the revolutionary FreeStyle Libre technology with insulin dosing information for future smart pens, insulin titration apps, and cloud software.

"For close to a century, Sanofi has been supporting those living with diabetes through our robust portfolio of medicines. This strategic relationship with Abbott is representative of the next evolution of our commitment for better diabetes care by incorporating digital tools into the daily life of people living with diabetes," said Gustavo Pesquin, Senior Vice President Global Diabetes and Cardiovascular Franchise at Sanofi. "By partnering with Abbott, we are a step closer to realizing our connected ecosystem, which would help improve control and the quality of life decision cycle for patients through individualized glycemic management of diabetes."

The non-exclusive collaboration will initially enable data sharing, at the consent of the user, between Abbott's FreeStyle Libre mobile app and cloud software and Sanofi's connected insulin pens, apps and cloud software that are currently in development. This data sharing will enable both people with diabetes and their doctors to make better informed treatment decisions around medication, nutrition and lifestyle.

"As the global leader in continuous glucose monitoring, we see a significant opportunity to impact the health of millions of people living with diabetes by developing new tools and connectivity with Sanofi, a leader in the insulin space," said Jared Watkin, Senior Vice President, Diabetes Care, Abbott. "Diabetes can be overwhelming as it is an information-rich condition with various streams of data from multiple devices. Building a digital ecosystem around FreeStyle Libre simplifies the user experience by consolidating how people get their data – both through offering Abbott's digital health tools and by working with other diabetes and technology leaders."

Sanofi is currently working to provide connected pens, apps and cloud software that will be compatible with the FreeStyle Libre system and its compatible digital health tools. The two companies aim to bring this to people with diabetes within the next few years, pending local regulatory approvals.

Abbott's FreeStyle Libre, the No. 1 sensor-based glucose monitoring system used worldwide, reads glucose levels through a sensor that can be worn on the back of the upper arm eliminating the need for fingersticks. FreeStyle Libre has changed the lives of more than 1.5 million people across 46 countries, and has secured partial or full reimbursement in 33 countries, including France, Ireland, Japan, the UK, and the US.

Abbott's FreeStyle LibreLink app enables users to capture and view their real-time glucose levels, their 8-hour glucose history, and how their glucose is currently changing on their smartphone. LibreView is a secure cloud-based diabetes management system that gives people with diabetes and healthcare professionals clear, easy-to-understand reports from the FreeStyle Libre system. LibreLinkUp is an app that enables caregivers of people living with diabetes to remotely monitor their loved ones' glucose readings.

AC Immune Receives Milestone Payment in Connection with Initiation of a Phase 2 Trial

AC Immune SA recently announced it has received a milestone payment from its partner Life Molecular Imaging in connection with the initiation of a Phase 2 study of the Tau positron-emission tomography (PET) tracer PI-2620.

PI-2620 is a next-generation Tau PET tracer developed using AC Immune's proprietary Morphomer discovery platform in a research collaboration with Life Molecular Imaging. It binds to Tau deposits which, along with beta-amyloid plaques, represent a critical pathological hallmark of Alzheimer's disease (AD). Tau deposits also play an important role in other neurodegenerative diseases.

The Phase 2 longitudinal study is being conducted in the UK and is expected to last approximately three years, with the overall goal being to evaluate PI-2620 as a targeted radiopharmaceutical for the detection of Tau deposits in the human brain. The data generated are intended to be used for obtaining regulatory approval in the US and Europe.

Prof. Andrea Pfeifer, CEO of AC Immune SA, said "The clinical advancement of PI-2620 is based on its excellent properties and imaging characteristics, and it further reinforces the proficiency of AC Immune's Morphomer™ technology and our ability to establish highly productive partnerships with well-respected companies such as Life Molecular Imaging. Treating earlier and targeting Tau are both key elements of our Roadmap to Successful Therapies for Neurodegenerative Diseases.

"There is a growing body of clinical evidence that Tau pathology drives disease progression, and this new Phase 2 trial further broadens AC Immune's world leading anti-Tau clinical pipeline, which also includes therapeutic antibodies (partnered with Roche/Genentech), small molecule inhibitors (partnered with Eli Lilly), and vaccines (partnered with Janssen). We are advancing these programs in parallel to generate robust clinical data, having most recently vaccinated the first patient in a Phase 1b/2a study of our clinically advanced anti-phospho-Tau vaccine candidate ACI-35.030."

The open label Phase 2 study will evaluate the safety and imaging characteristics of PI-2620 as a PET radioligand for imaging Tau deposition in the brains of patients with mild cognitive impairment (MCI) and mild to moderate AD in comparison with non-demented control (NDC) participants.

PI-2620 was discovered and developed in a research collaboration between AC Immune and Life Molecular Imaging. It has demonstrated robust brain uptake and fast wash-out in non-target regions, a broad imaging window between 30 and 90 minutes post-injection (p.i.) for AD, and excellent reproducibility between test and retest scans. The absence of significant off-target binding enables PI-2620 to detect and quantify early Tau deposition in the brain. PI-2620 also shows promise for non-AD Tauopathies like progressive supranuclear palsy (PSP). Life Molecular Imaging has the exclusive, worldwide license for research, development and commercialization of Tau PET tracers generated within the discovery program.

InveniAI Launches Suite of Products Powered by Artificial Intelligence Platform

InveniAI Corporation recently announced the expansion of its flagship AI- and ML-driven innovation monitoring platform, AlphaMeld. This expansion will provide a suite of products to facilitate the democratization of data analysis across the life sciences value chain and tap into InveniAI's extensive domain expertise and curated data sets that have been aligned with industry specific algorithms.

CIMeld, an AlphaMeld powered product, was launched at the PharmaCI USA 2019 Conference and Exhibition held September 18-19, where competitive intelligence executives in pharma, biotech, and medical devices meet at one of the largest CI assemblies in the world. CIMeld is a unique product that takes advantage of the digital data deluge and leverages AI-powered technology to triangulate signals from multiple sources to generate insights and identify opportunities and threats across diseases, companies, drug portfolios, and early innovation.

The AlphaMeld suite of products is accessible via a secure, customized, cloud-based interface with the option to personalize the definition of success and failure that lends a unique competitive advantage to its users. In addition to competitive and business intelligence insights, the AlphaMeld suite of products addresses innovation bottlenecks in the life sciences including, identification of the earliest signals of emergence for target identification and validation, technology innovations, and clinical innovations that identify drugs with high probability of clinical success. Together with InveniAI's broad domain expertise, stakeholders can leverage an integrated platform built on 15 years of data sets that have been cleaned, curated, connected and customized with AI/ML algorithms to address specific business questions – bridging the gap between human expertise and the insights hidden in the vast amounts of data being generated both within an organization or in the public domain.

"With the rapid uptake of AlphaMeld's technology, and based on customer feedback, we have created a product line that has broad stakeholder appeal within the life sciences," said Krishnan Nandabalan, PhD, President, and CEO of InveniAI. "Our platform is commercially validated with multiple clinical candidates – the most advanced program will be entering pivotal trials and numerous other programs entering human proof of concept trials."

AlphaMeld, created on the premise that every innovation begins with a core discovery or invention that gathers momentum, is an AI-based platform powered with machine learning algorithms that monitor alpha signals indicative of breakthrough innovation. The platform operates in real-time and recognizes these patterns in a rapidly changing and diverse data environment by engaging internal experts to personalize the definition of success and failure for an organization or vertical market. The platform eliminates dependence on a time-series and uses industry-aware scoring algorithms that are customized and further strengthened by incorporating continuous feedback through machine learning. AlphaMeld is trained to amplify human expertise to enable robust decision-making tailored to the needs of multiple stakeholders within an organization.

DURECT Earns $10-Million Milestone Payment From Gilead

DURECT Corporation recently announced that further development of a long-acting injectable HIV investigational product utilizing DURECT's SABER technology has triggered a $10-million milestone payment from Gilead Sciences, Inc. to DURECT under the license agreement between the companies.

"We are pleased that Gilead has been rapidly advancing this program," stated James E. Brown, President and CEO of DURECT. "We believe that long-acting injectables using our SABER platform have the potential to improve the lives of people with HIV."

"Our license agreement with Gilead is part of DURECT's broader strategy to enter into selective collaborations and other arrangements for our technologies and product development programs," continued Dr. Brown. "By leveraging our resources with corporate collaborators, we believe we can retain commercial interest in multiple product candidates and maximize value for our shareholders."

In July 2019, DURECT and Gilead entered into an agreement granting Gilead the exclusive worldwide rights to develop and commercialize a long-acting injectable HIV product utilizing DURECT's SABER technology. Under the terms of the agreement, Gilead made an upfront payment to DURECT of $25 million, and further development has triggered an additional $10-million milestone payment. Remaining milestones include the potential for up to an additional $65 million in development and regulatory milestones, up to an additional $70 million in sales-based milestones, as well as tiered royalties on product sales. Gilead also received exclusive access to the SABER platform for HIV and hepatitis B virus (HBV) and the exclusive option to license additional SABER-based products directed to HIV and HBV for an additional $150 million per product in upfront, development, regulatory, and sales based milestones as well as tiered royalties on sales. The parties will collaborate on specified development activities with Gilead controlling and funding the development programs.

DURECT's SABER Technology (Sucrose acetate isobutyrate extended release) is a patented technology designed to provide sustained release for long-acting injectable products. The SABER technology is also the basis of POSIMIR (bupivacaine extended-release solution under investigation for the management of post-operative pain).

DURECT is a biopharmaceutical company actively developing therapeutics based on its Epigenetic Regulator Program and proprietary drug delivery platforms. DUR 928, a new chemical entity in Phase 2 development, is the lead candidate in DURECT's Epigenetic Regulator Program. An endogenous, orally bioavailable small molecule, DUR-928 has been shown in preclinical studies to play an important regulatory role in lipid homeostasis, inflammation, and cell survival. Human applications may include acute organ injury such as alcoholic Hepatitis (AH) and acute kidney injury (AKI), chronic hepatic diseases such as nonalcoholic steatohepatitis (NASH), and inflammatory skin conditions such as psoriasis and atopic dermatitis. DURECT's advanced oral and injectable delivery technologies are designed to enable new indications and enhanced attributes for small-molecule and biologic drugs.

Minerva Neurosciences & Catalent Enter Commercial Supply Agreement

Minerva Neurosciences, Inc. and Catalent recently announced they have entered into a long-term commercial supply agreement for Roluperidone (MIN-101), an investigational compound under development by Minerva for the treatment of negative symptoms of schizophrenia. Under the terms of the agreement, Catalent will manufacture and package the finished dose form of the drug at its facility in Schorndorf, Germany.

Negative symptoms can persist chronically throughout the lifetime of patients with schizophrenia and contribute to poor quality of life and functional outcomes. No treatment is approved to treat these symptoms in the US. Minerva is currently conducting a pivotal Phase 3 clinical trial with roluperidone at sites in Europe and the US and could potentially be the first to market.

"Launching any new drug with a partner marks the culmination of many years of hard work and having to overcome challenges, and is a milestone for a project," said Aris Gennadios, PhD, President, Catalent Softgel & Oral Technologies. "Catalent has a proven track record in developing new treatments and bringing them to market quickly, efficiently, and in the most patient-friendly dose form; and we are pleased to partner with Minerva on this important potential therapy."

"We are pleased to be working closely with our partner, Catalent, under a long-term supply agreement for a compound with the potential to treat negative symptoms, one of the leading unmet needs in schizophrenia," said Rick Russell, President of Minerva Neurosciences.

To date, Catalent has worked with Minerva to undertake the tech transfer from pilot to commercial-scale production. This included analytical methods transfer and validation, process optimization, stability studies, and registration batch manufacturing; as well as packaging studies, and assessing the influence of formulation factors on the product's critical quality attributes as required by Quality by Design (QbD) process.

Catalent is the leading global provider of advanced delivery technologies, development, and manufacturing solutions for drugs, biologics, gene therapies, and consumer health products. With over 85 years serving the industry, Catalent has proven expertise in bringing more customer products to market faster, enhancing product performance and ensuring reliable global clinical and commercial product supply. Catalent employs nearly 13,000 people, including approximately 2,400 scientists, at more than 35 facilities across five continents, and in fiscal year 2019 generated over $2.5 billion in annual revenue.

Minerva Neurosciences, Inc. is a clinical-stage biopharmaceutical company focused on the development and commercialization of a portfolio of product candidates to treat CNS diseases. Minerva's proprietary compounds include: roluperidone (MIN-101), in clinical development for schizophrenia; seltorexant (MIN-202 or JNJ-42847922), in clinical development for insomnia and major depressive disorder (MDD); MIN-117, in clinical development for MDD; and MIN-301, in pre-clinical development for Parkinson's disease. Minerva's common stock is listed on the NASDAQ Global Market under the symbol "NERV."

Aptevo Therapeutics Introduces New Adaptir Bispecific Antibody Candidate

Aptevo Therapeutics Inc. recently introduced a new immuno-oncology candidate, APVO603, built on Aptevo's proprietary ADAPTIR bispecific antibody platform. Jane Gross, PhD, Chief Scientific Officer for Aptevo, presented preclinical data on APVO603 in an oral presentation at the 10th Annual World Bispecific Summit in Waltham, MA.

APVO603 is a dual agonist bispecific antibody employing a novel mechanism of action to simultaneously target 4-1BB (CD137) and OX40 (CD134), both members of the TNF-receptor family. Dual targeting of 4-1BB and OX40 provides synergistic co-stimulation of T cells with the potential to amplify the cytotoxic function of activated T cells and NK cells, potentially leading to more robust anti-tumor responses.

"Aptevo continues to create new, innovative molecules based on our ADAPTIR platform technology and we are excited to introduce our newest bispecific antibody candidate, APVO603," said Dr. Gross. "APVO603 demonstrates the versatility and flexibility of our ADAPTIR platform to generate multiple candidates with diverse mechanisms of action (T-cell engagers, T-cell co-stimulators and targeted cytokines) for the treatment of cancer and autoimmune diseases. Importantly, this flexibility allows us to engineer novel molecules addressing both hematological cancers and solid tumors – a significant area of unmet medical need within the field of immuno-oncology therapeutics."

"Bispecific antibodies are expected to be the cornerstone of the next generation of immuno-oncology products," Dr. Gross continued. "The key to success is having a technology and the necessary expertise to generate bispecifics with the desired activity, while maintaining excellent stability, half-life and manufacturing characteristics. Our demonstrated ability to create new molecules with novel function substantiates the power and versatility of the ADAPTIR platform."

APVO603 is an optimized, next-generation bispecific antibody candidate designed to simultaneously target 4-1BB and OX40 to bolster activation of CD4 and CD8 T cells and Natural Killer cells to enhance anti-tumor immune responses to tumors. APVO603 was built on Aptevo's proprietary ADAPTIR protein therapeutic platform.

Focused on generating novel, targeted bispecific antibody-based immunotherapies for cancer and autoimmune diseases, the ADAPTIR platform offers key advantages over other bispecific formats, derived in part from the flexible and modular nature of the ADAPTIR structure. These advantages include: the potential to achieve potent biological activity; desirable manufacturability characteristics, and promote an extended half-life. In preclinical studies, ADAPTIR CD3-based T-cell engagers achieve potent T-cell tumor cytotoxicity with reduced T-cell cytokine release compared to other bispecific platforms. The flexible ADAPTIR platform allows Aptevo to build candidates with diverse mechanisms of action, including Redirected T-Cell Cytotoxicity (RTCC); T-cell co-stimulation, and targeted cytokine release. Two ADAPTIR molecules (APVO436 targeting CD123 and CD3 for treatment of AML and other hematologic diseases, and APVO210, a targeted cytokine therapeutic for treatment of multiple autoimmune diseases) are currently in clinical development. A third candidate, ALG.APV-527, (targeting 4-1BB and 5T4, a solid tumor antigen) and APVO603 (4-1BB and OX40) are in preclinical development.

Wave Life Sciences Announces Fast Track Designation from US FDA

Wave Life Sciences Ltd. recently announced the US FDA has granted Fast Track designation to suvodirsen for the treatment of Duchenne muscular dystrophy (DMD) in patients amenable to exon 51 skipping. The designation was based on comprehensive in vitro and in vivo nonclinical data that support the potential for suvodirsen to address a significant unmet medical need.

Suvodirsen is currently being evaluated in an ongoing open-label extension (OLE) study for DMD patients amenable to exon 51 skipping. Wave remains on track to deliver an interim analysis of dystrophin expression from muscle biopsies in boys receiving suvodirsen in the OLE study in the fourth quarter of 2019. Pending positive clinical dystrophin expression data, the company expects to file for an accelerated approval of suvodirsen in the US in the second half of 2020. Suvodirsen is also currently being studied in DYSTANCE 51, a global Phase 2/3, multicenter, randomized, double-blind, placebo-controlled trial that will evaluate the efficacy and safety of suvodirsen. Results from the DYSTANCE 51 trial are intended to support global regulatory filings for suvodirsen. The study is also the first ever selected by the FDA for its Complex Innovative Trial Design (CID) pilot program.

Suvodirsen has also been granted orphan drug designation for the treatment of DMD by the FDA and the European Commission, as well as rare pediatric disease designation by the FDA. In addition to suvodirsen, Wave continues to advance WVE-N531, its preclinical candidate to treat DMD in boys amenable to exon 53 skipping. The company is also exploring exon targets beyond those targeted by suvodirsen and WVE-N531, including exons 44, 45, 52, 54, and 55.

Suvodirsen is an investigational stereopure oligonucleotide currently being evaluated in an ongoing open-label extension (OLE) study for the treatment of boys with Duchenne muscular dystrophy (DMD) who are amenable to exon 51 skipping. Suvodirsen is also being a studied in DYSTANCE 51, a global Phase 2/3, multicenter, randomized, double-blind, placebo-controlled trial that will evaluate the efficacy and safety of suvodirsen.

Approximately 13% of DMD patients have genetic mutations that are amenable to treatment with an exon 51 skipping therapy. Exon-skipping technology has the potential to induce cellular machinery to 'skip over' a targeted exon and restore the reading frame, resulting in the production of internally truncated, but functional dystrophin protein.

Duchenne muscular dystrophy (DMD) is a fatal X-linked genetic neuromuscular disorder caused predominantly by out-of-frame deletions in the dystrophin gene, resulting in absent or defective dystrophin protein. Dystrophin protein is needed for normal muscle maintenance and operation. Because of the genetic mutations in DMD, the body cannot produce functional dystrophin, which results in progressive and irreversible loss of muscle function, including the heart and lungs. Worldwide, DMD affects approximately one in 5,000 newborn boys.

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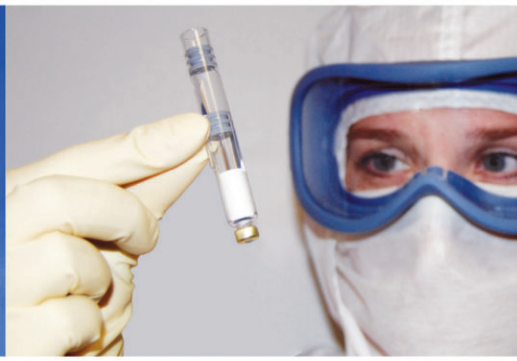

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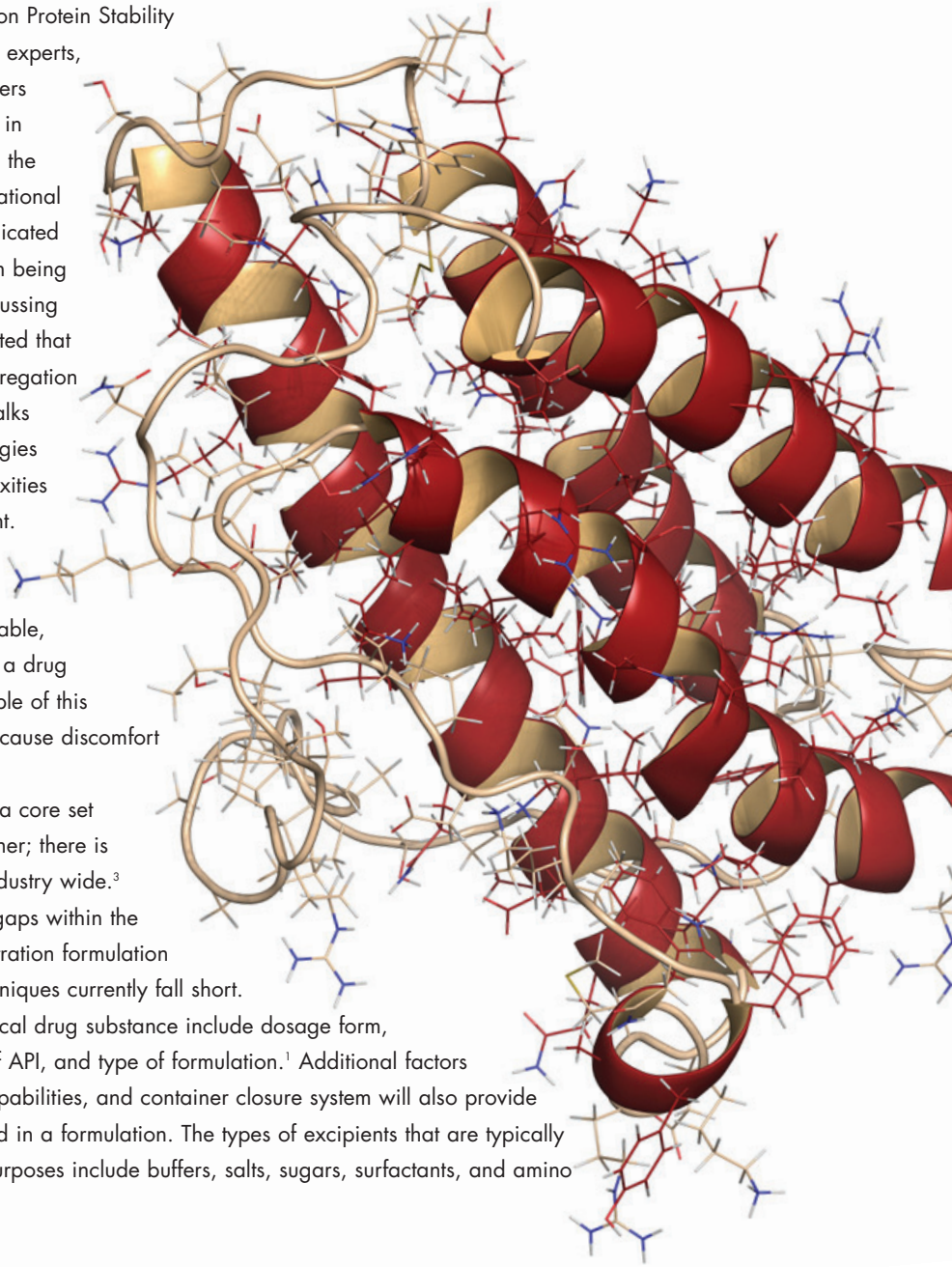
Characterization Corner

A New Weapon in Formulation Development

By: Matt McGann, Field Applications & Marketing Manager,
RedShift BioAnalytics, Inc.

At the 2019 Colorado Conference on Protein Stability held in Breckenridge CO, industry experts, key opinion leaders, and researchers gathered to discuss challenges and advances in formulation development of biologics. Among the work presented, several studies using computational modeling to elucidate formulation stability indicated that our understanding is still a long way from being prescriptive in formulation design. When discussing aggregation and amyloidosis, it was highlighted that the role of reversible self-association and aggregation is far more complex than envisioned. Many talks highlighted the breadth of analytical technologies that are being used to understand the complexities of biopharmaceutical design and development. A significant observation throughout the conference was that sometimes the most stable formulation is not, in fact, the most suitable, as it is ultimately more important to formulate a drug product that is fit for purpose.[1] A good example of this is the use of citrate buffer, which is known to cause discomfort at the injection site in patients.[2]



Formulation development scientists have a core set of technologies used by almost every researcher; there is however no standard set of protocols used industry wide.[3] It is also evident there are several analytical gaps within the toolset, particularly in relation to high-concentration formulation development, where nearly all analytical techniques currently fall short.

Critical factors in the design of a biological drug substance include dosage form, concentration, route of administration, type of API, and type of formulation.[1] Additional factors related to manufacturing process, fill-finish capabilities, and container closure system will also provide limitations on what can and cannot be utilized in a formulation. The types of excipients that are typically used for stability, solubility, and pH control purposes include buffers, salts, sugars, surfactants, and amino

acids. Additionally, excipients such as antioxidants and preservatives can be added to ensure the shelf-life of the product.[1]

When assessing the suitability of a formulation, there are generally three aspects that need to be considered:

1) Colloidal stability, a measure of the interactions between proteins in solution, and between proteins and the solvent. These interactions can be based on hydrogen bonding, Van der Waals interactions, and dipole-dipole interactions. Repulsive interactions between particles, measured by a positive diffusion interaction parameter (kD) and second virial coefficient (B22) are generally considered to be two primary indications of such stability. Additionally, physical charge measurements, such as effective charge (Zeff) or isoelectric point (pI), can be used to assess colloidal stability.

2) Chemical stability, a measure of the resistance of the protein to chemical denaturation processes, such as oxidation, deamidation, and disulphide cross-linking. The development of charge variants of a protein as a result of any of these processes can be observed using techniques such as capillary isoelectric focusing. Additionally, aggregation temperature and the molecular weight envelope of a protein can highlight changes in chemical structure. Most of these techniques can be measured in a high-throughput or at least in a fully automated fashion, making them suitable for screening larger numbers of variations in a formulation set.

3) Measurement of conformational stability of formulated proteins by assessing melting temperature, or higher order structure poses a challenge in terms of both throughput and compatibility. Whilst DSF offers significant throughput, it only provides a global measure of the conformational stability of the structure.[4] Direct measurement of higher order structure using far-UV CD and FTIR provide information regarding the secondary structure of a protein; however, both have limitations. Circular dichroism works most effectively at concentrations less than 2 mg/mL and is not compatible with many excipients and buffers. FTIR, on the other hand, offers better chemical compatibility and concentration range; however, volume limitations and a lack of automation make it a challenge to implement.

With the requirements of formulation development of biopharmaceuticals becoming more demanding, evolution of analytical tools that can measure stability over a wide concentration range, in the presence of complex buffer systems is critical. Microfluidic Modulation Spectroscopy is an alternative technique that combines microfluidics with a high-power mid-infrared laser to quantify secondary structure across a concentration range of 0.1 to over 200 mg/mL in complex formulations. The technology provides higher order structure information in complex formulations without the need for dilution, buffer exchange, or chemical modification, and is the final addition in the biophysical characterization scientist's toolkit. ◆

TABLE 1

Function	Measure	Technique
Colloidal	k_D, B_{22}, R_H	Dynamic Light Scattering
	Z_{eff}	Electrophoretic Light Scattering
	pI	Capillary Isoelectric Focusing
Chemical	T_{agg}	Dynamic Light Scattering
	Charge Heterogeneity	Capillary Isoelectric Focusing
	Mw	Mass Spectrometry
	Glycan Analysis	
Conformational	Melting Point	Differential Scanning Fluorescence
	Higher Order Structure	Far-UV Circular Dichroism Fourier Transform Infrared Spectroscopy Raman Spectroscopy Nuclear Magnetic Resonance Spectroscopy Microfluidic Modulation Spectroscopy

Summary of the measured properties and analytical tools used in the development of a biopharmaceutical formulation.

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COMBINATION PRODUCT DEVELOPMENT

New Horizons in Development to Meet Emerging Demands

By: Ed Trappler and John A. Merhige, MEM

INTRODUCTION

The healthcare landscape has changed significantly throughout the past several years as the delivery of care has moved rapidly toward more economical and non-institutional settings. Just as many surgical procedures have moved from the hospital to the outpatient setting, the administration of injectable medications for chronic diseases has moved from formal healthcare settings to the home. This requires the product and delivery system to be conducive for non-healthcare professional users, self-injecting patients and their support system, to easily and successfully administer medications. This is reflected in the projections for the self-injections market to grow more than 22% annually toward $119 billion by 2024.[1] The course of therapy to treat chronic conditions is often an injected biologic, contributing to the forecasted growth for biologics of 10.9% CAGR to $480 billion in 2024.[2] Many of these biologics, such as plasma proteins, vaccines, monoclonal antibodies, and oligonucleotides, as well as some small molecules, require lyophilization because they are unstable as aqueous solutions. The lyophilized dried form provides suitable preservation for adequate long-term storage, yet requires conversion into an aqueous solution at the point of care.

The new expectation is to couple the needs of a course of therapeutic treatment with a patient-centric delivery system. In the emerging horizon, less- experienced users must deliver more complex formulations by using more sophisticated delivery systems. Thus, conventional approaches to product design, formulation, and manufacturing are quickly becoming antiquated. In today's environment, it is no longer sufficient to put a product in a vial. The future of healthcare products places increasing demands on the industry to provide innovations for delivering combination products. The dual-chamber reconstitution system is a prime example of a combination product that can meet the evolving industry and patient needs. The challenge is that such combination products will require clinical, device, formulation, and process innovation as well as collaboration within the supply chain. Credence MedSystems and Lyophilization Technology, Inc. (LTI) are collaborating closely to advance the development of a dual-chamber combination product offering to the industry.

SAFETY, USABILITY & TOTAL COST REQUIREMENTS FOR AN EFFECTIVE SOLUTION

Contemporary approaches to product design must consider essential aspects in delivering the needed course of therapy all the way to the patient; this includes patient safety, usability, and total cost. Requirements to design a combination product with a patient-centric perspective have implications on both the delivery device and the development of a lyophilized drug product.

Safety

It is essential the correct composition is delivered at the time of administration. Proper reconstitution requires a high level of accuracy and precision in the quantity of active and diluent to prepare the final injectable solution. The ideal product design to create an effective delivery system would ensure the correct composition by combining the active product formulation and diluent together in the same primary packaging. It is imperative to achieve proper and complete reconstitution; and reconstitution time is more critical in a dual- chamber product compared to a

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lyophilized product in a vial. This is integral to patient compliance because dissolution challenges or longer reconstitution times can increase the risk of an injection prior to forming a complete solution.

Opportunities also exist to improve the safety and reduce the complexity associated with the preparation of a conventional lyophilized product in a vial, which can commonly require over 15 steps to prepare for administration.[3] Such complexity introduces significant opportunities for error, the potential for needlestick injury, and the risk of contamination. Furthermore, a delivery device that automatically deactivates the needle following injection and prevents reuse of the system can further improve user safety.

Usability

Self-injectors need an intuitive, easy-to-use, and safe device to effectively deliver an injectable product and to have the greatest opportunity for patient compliance. Like the easy-to-open pill container for arthritic patients, an injectable delivery system must be readily activated and the product easily administered. Patient convenience and user preference must also be considered.

Traditionally, self-injectors are divided in their preference between using a syringe alone (a "naked" syringe), which provides more control, and using an autoinjector, which helps to automate the injection. This warrants developing a product that can be used alone as a syringe as well as within an autoinjector. Applicable to any injected product, ensuring the full dose is delivered is essential. Here again, designs of a syringe system and a compatible autoinjector both need to incorporate aspects to ensure proper dosing.

For a lyophilized combination product, there is a unique and demanding need to revert the dried product and diluent to form a complete solution. Complete diluent transfer is critical. The means in which the diluent is presented to the API may also be a factor. Complete "wettability" with full distribution and exposure of the dried product to the diluent is imperative. With products that are shear sensitive, such as some polypeptides and proteins, the velocity of diluent introduction can create irreversible denaturation. All of these factors must be considered in the diluent transfer and delivery device design.

FIGURE 1

The Main Components Commonly Required in a Conventional Lyophilization Reconstitution Kit

Total Cost

Conventional presentations of a lyophilized product in a vial can require multiple vials, syringes, needles, and vial adapters, as well as ancillary components like cotton swabs or sanitizing wipes. Figure 1 shows a representative example of the several components needed for preparing and delivering a conventional lyophilized preparation. To support the conventional product throughout the supply chain, this presentation requires a greater logistical burden to our healthcare system for the cost of managing and maintaining inventory, distribution, storage, packaging, and materials. Additionally, in a formal healthcare setting, the time and effort to navigate the complex preparation process discussed earlier must be factored into the total cost of delivering the drug to the patient. Finally, the cost of overfilling, and adverse events related to needlestick, inaccurate dosing, mishandling, or contamination, represent meaningful factors when assessing the total cost of drug delivery.

ACHIEVING A SAFE, EFFECTIVE & EASY-TO-USE PATIENT-CENTRIC DRUG DELIVERY SYSTEM

Meeting the needs for a patient-centric reconstitution and delivery system requires innovation in delivery system design, formulation, and process engineering. The requirements are affected by factors, such as product indication, drug product characteristics, and injection volume. The setting for product use is another important factor; requirements differ in specialty applications, such as ambulatory and institutional emergency, dermatology, and ophthalmology, when compared to self-administration in the home. As such, enhanced design and device flexibility allows for development of combination products most suited for their intended use.

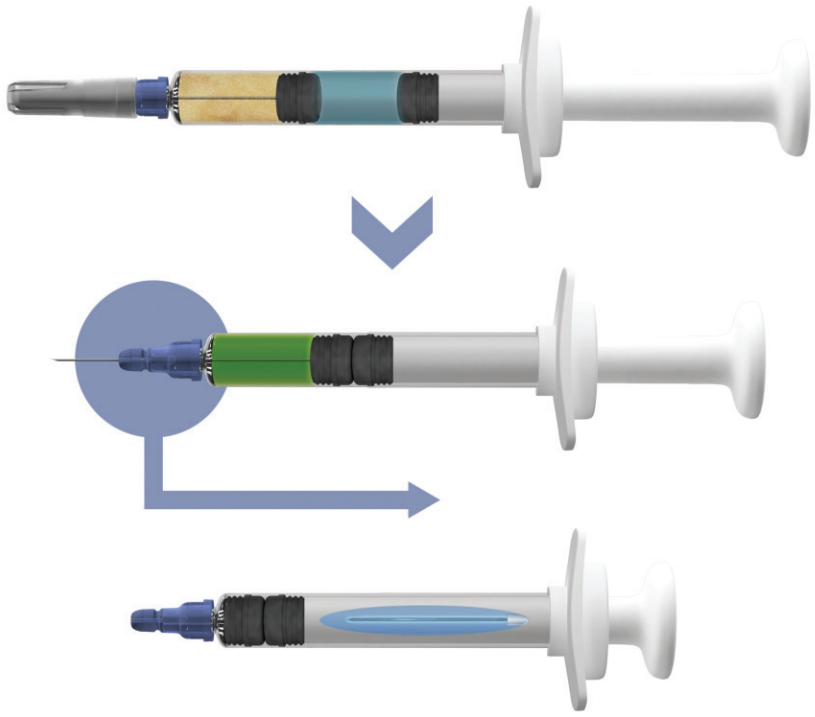
Delivery System Design

An example of a dual-chamber lyophilized product delivery system designed to be patient-centric is the Companion® Dual Chamber Reconstitution Syringe. By storing the lyophilized product with the diluent in a single primary packaging device that is also the delivery system, the Companion® Dual Chamber provides the required storage conditions while maximizing the safety, effectiveness, and ease-of-use for a patient administering lyophilized medications.

The Companion® Dual Chamber allows use of a standard syringe or cartridge barrel and standard plunger, preserving the use of preferred commercially available primary package components. The design eliminates the presence of the adhesive conventionally used to affix a staked needle into a syringe barrel, thereby removing a substance that risks detrimental impact to the product. The system and technology are compatible with multiple syringe barrel sizes, bringing the advantages of optimized package size and improved ergonomics. This is increasingly important as injection volumes for subcutaneous (Sub-Q) administration get larger. Historically in the 1.0-mL range, we are now seeing higher volumes injected Sub-Q; Sanofi's Dupilumab, a 2-mL Sub-Q abdominal injection, is a prime example.

Use of the Companion® Dual Chamber device entails two straight-forward steps for preparing and administering a lyophilized drug product. In the first step, the user pushes on the plunger rod to readily transfer diluent from the rear to the front chamber, reconstituting the lyophilized cake to form a solution. As seen in Figure 2, an internal transfer path eliminates the need for an external bypass for the glass barrel. Once reconstitution is complete, the user continues to press the plunger rod to administer the injection until a tactile and audible end-of-dose click confirms that the full dose has been delivered. The needle then retracts seamlessly into the plunger rod, protecting the user and disabling the syringe from reuse. This dual-chamber system consolidates multiple features into one device: reconstitution; user-feedback; passive needlestick safety; reuse prevention; and the familiarity of a staked-needle syringe that allows conventional syringe operation.

FIGURE 2



Use of the Companion® Dual Chamber Reconstitution System

Further flexibility is provided in that the Companion® Dual Chamber can also be combined with a user-attached needle or used with needleless adapters. A user-attached needle is suited for intramuscular (IM) injections when the preferred needle size is chosen at the time of injection, while the needleless version is more suitable for delivering the reconstituted solution into an IV bag or line for intravenous administration. The assembled Companion® Dual Chamber Syringe can also be incorporated into an autoinjector, allowing the same primary package to be used as a "naked" syringe or in device-assisted administration. This design platform offers sufficient flexibility for multiple applications as listed earlier. The Credence Companion® Dual Chamber Reconstitution System presents a safe and effective way to allow both non-professional users and healthcare providers alike to safely and more easily deliver lyophilized drug products in various settings.

Formulation Development

There are several considerations in developing the formulation for a product housed in a combination product delivery system. The Quality Target Product Profile (QTPP), a precursor to the finished product Critical Quality Attributes (CQA), must be expanded beyond that for a product presented to a clinician in a vial. In addition to stabilizing the drug substance in both

the liquid and solid states, the reconstituted solution must be immediately suitable for injection. This places more rigorous requirements when developing a formulation. It is most desirable that formulation constructs be isotonic and at or near physiological pH. The choice of excipients is also more critical than those for a vial-based product. For example, if a citric acid/sodium citrate buffer is the best choice for control of pH and optimal stability, there is a limit to the buffer concentration for a Sub-Q administration to avoid irritation at the injection site.

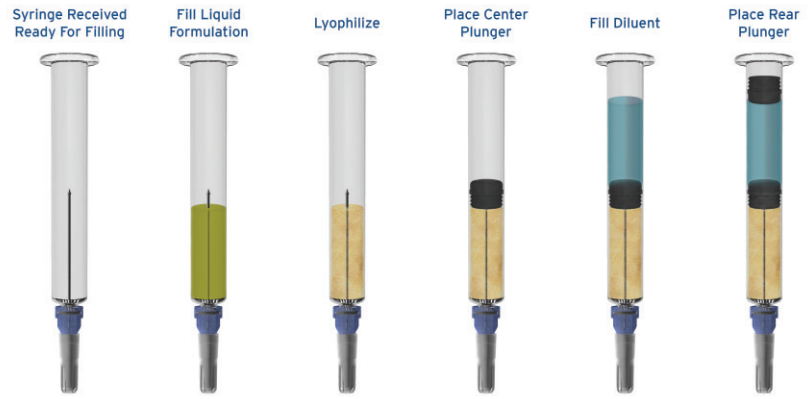
Specific excipients may be needed to improve drug substance solubility and dissolution. It is important to recognize there may be both a salting-in and salting-out effect. There may also be a strong influence of the formulation on reconstitution time. With a vial-based product, a reconstitution time of 2 minutes is readily accommodated, but this is unsuitable for a syringe. Reconstitution needs to be in the range of several seconds to enable better patient compliance, and instantaneous reconstitution is preferred. It is also important to consider compatibility of the formulation construct with silicone on the barrel and plunger.

Process Engineering

Figure 3 represents a method of filling/lyophilizing in the Companion® Dual Chamber Syringe that has supply chain and processing efficiencies. Unique to lyophilization, the geometry of the primary packaging has a significant impact on heat transfer, one of the rate-limiting factors for the process. With a conventional vial, the contour of the vial bottom and contact with the lyophilizer shelf is a key aspect of enabling heat transfer. The geometry of a syringe, and specifically the limited contact area with the lyophilizer shelf, makes the obtainable heat transfer a fraction of that relative to a vial. Therefore, the syringe needs to be processed in a specifically designed tray. To process the range of products including biopharmaceuticals, which tend to have a low critical threshold temperature for freezing and primary drying, the processing tray must satisfy the needs of aseptic processing as well as heat transfer during lyophilization. Figure 4 depicts the configuration of a specialized tray designed specifically for aseptic processing and lyophilization in dual chamber devices.

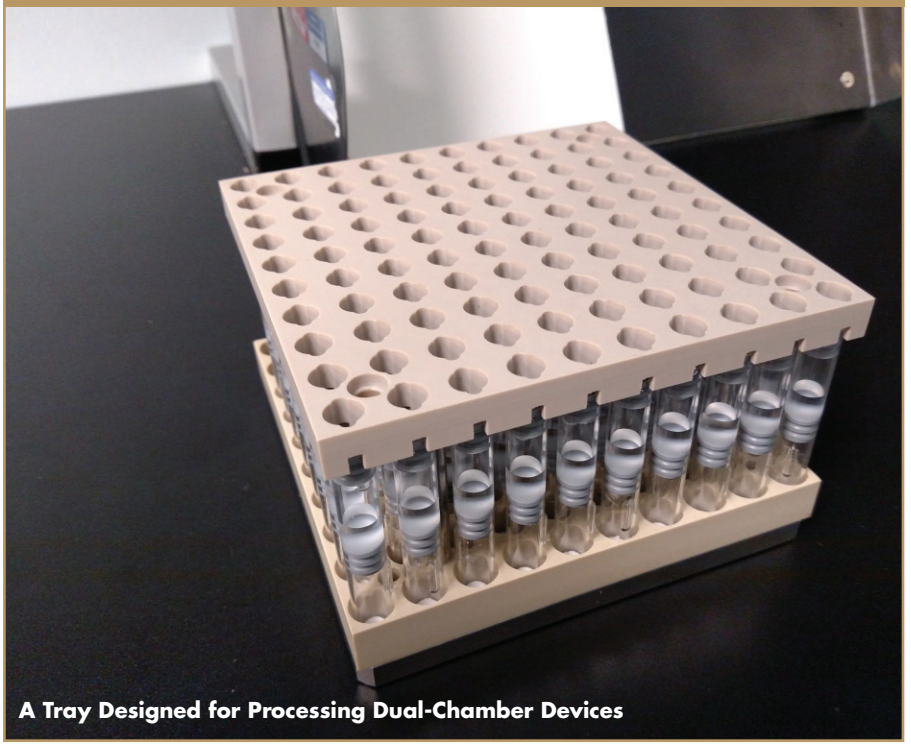
The syringe geometry also influences the height of the dried cake, which has a significant impact on the lyophilization process due to mass transfer of the water vapor from the sublimation of ice. The water vapor generated as the ice sublimes in primary drying must traverse through the dried layer above the sublimation front. The greater this height, and therefore the distance the water vapor needs to travel,

FIGURE 3



Processing in the Companion® Dual Chamber Syringe

FIGURE 4



A Tray Designed for Processing Dual-Chamber Devices

the more resistance to the water vapor traveling through the dried layer above the sublimation front.

COLLABORATION IN THE SUPPLY CHAIN: INTEGRATING A UNIQUE COMBINATION PRODUCT INTO COMMERCIAL MANUFACTURING

Coupling expertise in drug product and process with that of drug delivery devices is essential to provide an innovative therapeutic to the industry, and most importantly, to the patient. The collaboration between Credence, a device developer and supplier, and LTI, a contract development and manufacturing organization, is a good example of a cooperation bringing value to the industry and its patients. The companies have collaborated to advance development of the dual-chamber product and associated fill-finish activities for both large and small pharma companies. To date, the collaboration has been focused on preclinical to early clinical development activities. The effort focuses on requirements beyond supporting the conventional development and product stability, including regulatory considerations, such as human factors and clinical studies.

Simply stated, if you do not have a product that can be manufactured at the scale required, you do not have a product. Development and manufacturing in the conventional presentation, in which a lyophilized product and diluent are in separate vials, are well established. Combining the preclinical and clinical drug product with the delivery device development presents distinctive challenges in advancing a combination product to the market. The collaboration between Credence and LTI is enabling achievement of development objectives in product design, formulation development, and equally important, engineering of the manufacturing process. Expanding to full production includes incorporating larger scale CMOs for commercial fill/finish, and collaboration with syringe manufacturers to integrate Companion® technology in the classic "ready-for-filling" configuration. Collaboration has been a key driver of the progress to date, and further collaboration in the supply chain is essential to achieve the goal: providing the patient a product that is effective in treating the condition and suitable for safe and proper administration in the chosen care setting. ◆

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BIOGRAPHIES

Ed Trappler has over 40 years of experience in lyophilization that includes product development, toxicology and clinical supply manufacturing, and parenteral production. In 1992, he founded Lyophilization Technology, Inc. as a source of scientific and technical services, expanding the knowledge and understanding of lyophilization. He has contributed to 6 books and authored and presented numerous papers and courses internationally. He has received numerous recognitions, is an active PDA member, serving as Chairperson of the Lyophilization Interest Group and Validation Task Force, and Education Advisory Board. The PDA awarded him the Gordon Personeous award for his contributions to the PDA and the James Agalloco award for education.

John A. Merhige is Chief Commercial Officer at Credence MedSystems, leading the company's business development, sales, and marketing strategies. Previously, he was Vice President, Market Development at Sanofi, which he joined upon its acquisition of Pluromed, where he was a member of the Executive Management team. He also founded Prelude Devices to identify and grow early stage medical technology ventures. He graduated from Dartmouth College with a Mechanical Engineering degree and returned to Dartmouth for a Masters in Engineering Management from the Thayer School of Engineering and the Tuck School of Business.

MICROFLUIDIC ENCAPSULATION

Controlling Drug Delivery With PLGA

By: Richard Gray, MA (Engineering)

ABSTRACT

Biocompatible and biodegradable polymers are frequently used in the pharma industry to encapsulate active pharmaceutical ingredients (APIs) and then degrade in the body over time, releasing the drug in a controlled way. However, the speed of drug delivery and release is affected by the size and shape of the particle, and strict control of these parameters is essential. Many companies are now taking a microfluidics approach to drug encapsulation, generating reproducible monodisperse particles and the advantages they offer. The following discusses the use of polymer microparticles for pharmaceutical applications, including specific examples of polylactic-co-glycolic acid (PLGA) encapsulation.

INTRODUCTION

Improving the delivery and release of drugs in the body has great potential to advance the treatment of a number of diseases. A key development has been the creation of therapies that can be delivered without systemic circulation, instead targeting localized areas. As a consequence, biodegradable polymers, such as PLGA, have gained in popularity in a number of biomedical areas, playing an important role in improving therapeutic treatments by enabling the encapsulation of APIs - such as drugs, antibiotics, growth factors, anti-inflammatories, peptides and proteins, nucleic acids, and radiotherapy agents - that can be delivered and released in a controlled way in the body. Encapsulation essentially offers protection to an API from enzymatic or acidic degradation in the stomach, improves diffusion of the drug across the digestive tract, and offers a way of introducing hydrophobic molecules into the body.

PARTICLE SYNTHESIS

Traditionally, the production of these types of particles has been conducted under batch conditions, but reproducibility is key, and this is difficult to achieve with these methods as they often produce a range of particle sizes. It is also simply not efficient to produce extremely small yields for single patients; a high number would be wasted and, in some cases (particularly those where radioactive therapeutics form the API), this leads to issues with disposal of hazardous materials. Instead, a microfluidic approach enables the continuous reproducible production of encapsulated therapeutics in uniformly-sized particles, created on demand in small numbers and tailored to the needs of each individual patient. These miniaturized reactions only require small amounts of reagents and drugs - which are often very expensive and in short supply - and the production volume can be easily scaled-up commercially using multiple chips in parallel.

Getting the therapeutic substance into the organic solvent can also prove difficult, as many APIs don't dissolve in organic solvents. Producing a powdered form of the therapeutic and suspending it in the solution is one method to overcome this (Figure 1), as is making a multiple emulsion (Figure 2), in which the drug is encapsulated within a water droplet inside the polymer outer droplet. Both of these methods can be challenging in batch processing, but are easily achieved using microfluidics, which offers more precise control over processing. It allows individual parameters, such as flow rates, polymer concentrations and ratios, drug load, solvent, and speed of production to be altered and fine-tuned, optimizing the reaction. The result is reproducible and monodisperse particles that release drugs in a controlled way, ensuring the correct dose is delivered within the therapeutic window, to maximum effect, and without unwanted side effects or toxicity.

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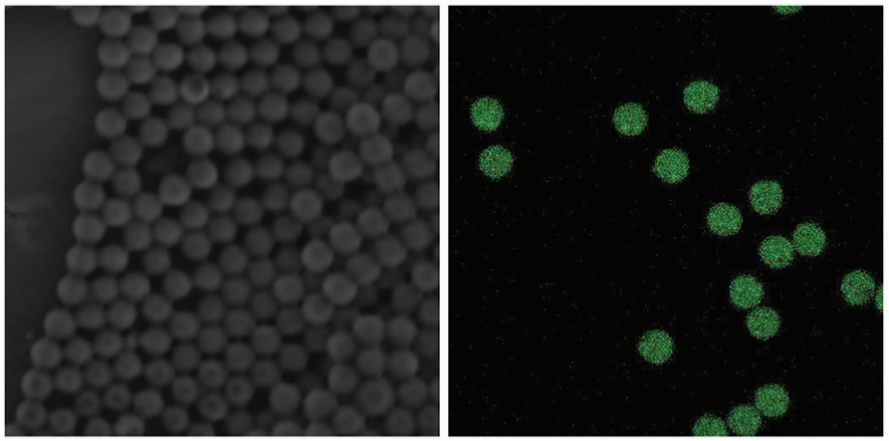
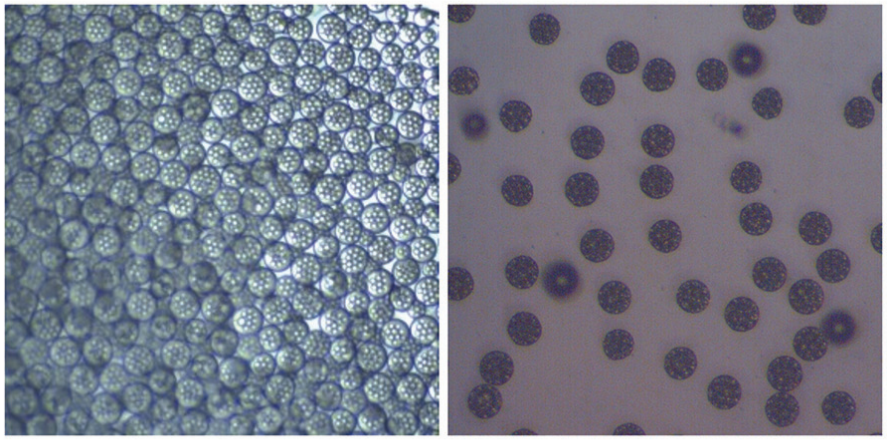
Reference
1 IMS Health. IMS Health Global Midas Edition. Danbury, CT: IMS Health Inc.; 2015.

FIGURE 1



Scanning electron microscopy (SEM) image of PLGA beads encapsulating powder API (left); fluorescence microscopy image of PLGA beads - green fluorescence indicates the positioning of the drug (doxorubicin).

FIGURE 2



Optical microscopy image of PLGA beads encapsulating water droplets containing API before (left) and after drying (right).

These benefits have led microfluidics to grow in popularity over recent years, not only in drug delivery, but in a range of applications.

THE USE OF PLGA

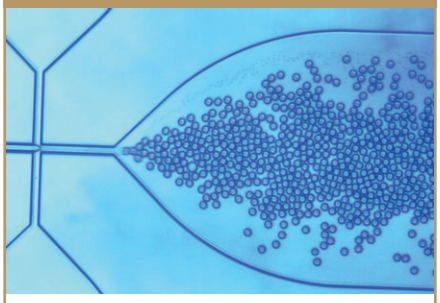
PLGA is already a commonly used biodegradable polymer approved by the FDA for the encapsulation of APIs and extensively used in a number of disease areas, from neurodegenerative and cardiovascular diseases to oncology, inflammatory disorders, and wound and bone healing. This is largely due to its biocompatibility, biodegradability, and controllable properties that can be modified to affect drug delivery and release. For instance, the polymer has been successfully applied to encapsulating radioisotopes for drug delivery, allowing radiation to be directly targeted at the exact tumor site. Optimizing the size and shape of the particles ensures the correct therapeutic dose and timely delivery - especially important when using elements with a short half-life.

To perform drug encapsulation, a solution of PLGA in an organic solvent is mixed with the chosen API, and the polymer is then solidified into a particle (Figure 3). However, the efficiency of entrapment and release is multi-layered and depends on the physicochemical properties of both the drug and the particle. This includes respective hydrophilicity and hydrophobicity, and particle size which, as it decreases, increases the surface-to-volume ratio, leading to quicker drug release. Balancing all of these factors is crucial to generating particles tailored to the needs of your patient.

PLGA DRUG DELIVERY SYSTEMS

A perfect example of this approach in action can be seen at the North West Centre for Advanced Drug Delivery (NoWCADD), based at the University of Manchester, where researchers are formulating PLGA drug delivery systems, using microfluidics to produce nanoparticles capable of a sustained drug release in oncology applications. The current focus is studying the use of commonly-used cancer drugs, such as SN-38, doxorubicin, and gemcitabine, to validate the system, before translating the approach for new drugs in the future. The aim of such a delivery system is to accumulate the API at the tumor site, localizing the therapeutic effect and controlling and sustaining drug release over time. This will minimize treatment administration, reduce side-effects, and increase efficiency. Additionally, NoWCADD is studying co-encapsulation in liposomes; their unique composition allows hydrophilic molecules to be loaded into the aqueous core, while lipophilic drugs can be incorporated into the lipid bi-

FIGURE 3



Water/PLGA in DCM droplets produced in the first 14 µm standard droplet hydrophobic chip.

layer. Often, cholesterol is also added as a supplementary component in the liposome membrane, as it increases thermal stability and reduces membrane permeability, promoting encapsulation and drug retention until release. This project is targeting breast cancer, as chemotherapy often uses combinations of drugs with different properties. PLGA conjugates well to most of the drug candidates regardless, and thus is ideal for this type of application.

Taking a microfluidics approach has enabled the researchers in Manchester to create and prepare different sizes of nanoparticles and control the encapsulation efficiency. It has also eliminated the batch-to-batch variability of production and improved the stability of the particles produced, with researchers able to quickly change parameters to optimize the formulation.

Dr. Annalisa Tirella, lecturer at the University of Manchester, said "The microfluidics system we are using is easy to use and robust, allows us to make both nano- and microparticle drug delivery systems, and has the advantage that we can use custom chips to optimize the performance of our processes. It is very flexible too; we can quickly and easily change parameters to test a prototype reaction using just a few microliters of a preparation, minimizing the costs involved. Importantly, the system gives us good control over our processes, eliminating batch-to-batch variation, which means that we can consistently and reliably produce nanoparticles. That's the really big benefit of the system."

Elsewhere, the School of Pharmacy at the University of Nottingham is also using PLGA to improve drug encapsulation and therapeutic delivery. This group is focusing on optimizing microfluidic reaction conditions to produce fluorescent PLGA particles. These particles will effectively act as biosensors that detect and monitor specific analytes in the body, and release biological medicines according to changes in the biochemical environment. A microfluidics approach allows strict control of both particle shape and size, along with drug release parameters, and has allowed the team to change one parameter at a time to alter the size, degradability, or profile of the particle. This is essential to ensure the correct dose and achieve maximum therapeutic benefit, without unwanted side effects.

Dr. Veeren Chauhan, Research Fellow at Nottingham, explained "The beauty of microfluidics is that, as the reactions are miniaturized, we only need small amounts of reagents and drugs, which are often quite expensive. It is also quite tunable, allowing us to selectively change individual parameters, such as flow rates, polymer concentrations and ratios, drug load, solvents, and the speed of production." Using this method, researchers have been able to produce a range of diverse PLGA particles in a monodispersed format to study the efficiency of entrapment, as well as drug release.

SUMMARY

The use of microfluidics is proving ideal for the production of PLGA particles for drug encapsulation and delivery, providing precise control that is vital for the efficient and effective production of uniform particles. Alterations to the particle can then be used to different effect, such as improving solubility or changing the target site. While there are already commercially-available products, continuous improvements in delivery nanosystems are opening up a range of translatable applications in other areas. An example of this is PLGA nanostructures that combine drug delivery, molecular imaging, and real-time monitoring of therapeutic response, which are paving the way for nanomedicine in the future. The use of PLGA and microfluidics is showing tremendous promise in drug delivery, and it will be exciting to see how this technology continues to grow. ◆

BIOGRAPHY

Richard Gray founded Syrris Ltd with Mark Gilligan in 2001, moving to the US in 2004 to manage the Group's US subsidiaries. Mr. Gray's background includes fast-track product and process development in consumer, medical device, and industrial sectors. Before Syrris, he was a General Manager in Mettler Toledo's Automated Chemistry Group, starting up and leading a 50-strong team in design and manufacturing of automated drug synthesis equipment. He worked in technical consulting at The Technology Partnership and PA Technology, and in helicopter rotor design at Westland Helicopters. He earned his MA in Engineering from Cambridge University and has a Diploma in Management Studies.

MODIFIED RELEASE

Alternative Strategies for Development of Modified-Release Dosage Forms

By: Andy Lewis, PhD

INTRODUCTION

Modified-release (MR) formulations are in high demand. For formulators, they enable drugs to be released in the optimal gastrointestinal (GI) locations to achieve and maintain desirable plasma concentrations for extended periods, avoiding undesirable excursions outside the therapeutic range. For patients, MR formulations provide the convenience of infrequent dosing with potentially greater efficacy and fewer side effects than similar, immediate-release delivery systems.

An impressive variety of MR formulations are possible, thanks to ongoing technological developments. Strategic selection of excipients and delivery technologies can yield MR formulations that fulfill very specific performance requirements, such as gastro-retention and sustained-, pulsatile-, or delayed-release formats.

Nonetheless, throughout the past 20 years, the fundamental methodology for developing these formulations has stagnated. Initial formulations continue to be founded upon *in vitro* and preclinical test results, despite evidence that these data correlate poorly with pharmacokinetic (PK) drug performance in humans.[1] The following will discuss a range of available formulation technologies, the challenges in MR formulation development, and the use of a design-space approach with on-demand manufacturing. This methodology enables critical-to-performance formulation adjustments during clinical conduct, saving time and cost, and reducing risk in MR drug development.

THE CHALLENGES OF MR FORMULATION

An ever-increasing number of polymers and formulation technologies allow finely tuned control of many aspects of drug release. Selecting and/or combining these technologies offers great potential for optimized oral drug delivery. However, managing all the variables and interpreting *in vitro*, preclinical, and available human clinical data to define a formulation strategy capable of achieving the desired PK performance is more difficult than many developers expect. Accurate performance prediction is crucial because miscalculations in planning for development or manufacturing are costly and often cause delays.

Abundance of Technology: A Blessing & a Curse

Off-the-shelf and proprietary polymers help MR developers achieve their PK goals. Certain polymers are better suited for sustained or delayed release and may be designed to deliver APIs to specific GI target areas, depending on physicochemical, biomechanical, and human physiological factors influencing the site of release. The range of solid dosage forms offers further layers of complexity. This ever-expanding array of tools makes many MR modalities possible. Some options are shown in Table 1.

Each delivery format has its own idiosyncrasies. In the first instance, understanding the target PK profile is crucial. What plasma concentration time profile does the formulation need to deliver? Experience and expertise are then required to select and implement a rational formulation program based upon API characteristics, such as solubility, stability in stomach acid, particle size, and bioavailability. Furthermore, human physiology factors (such as an absorption window, drug transporters, and enzymes

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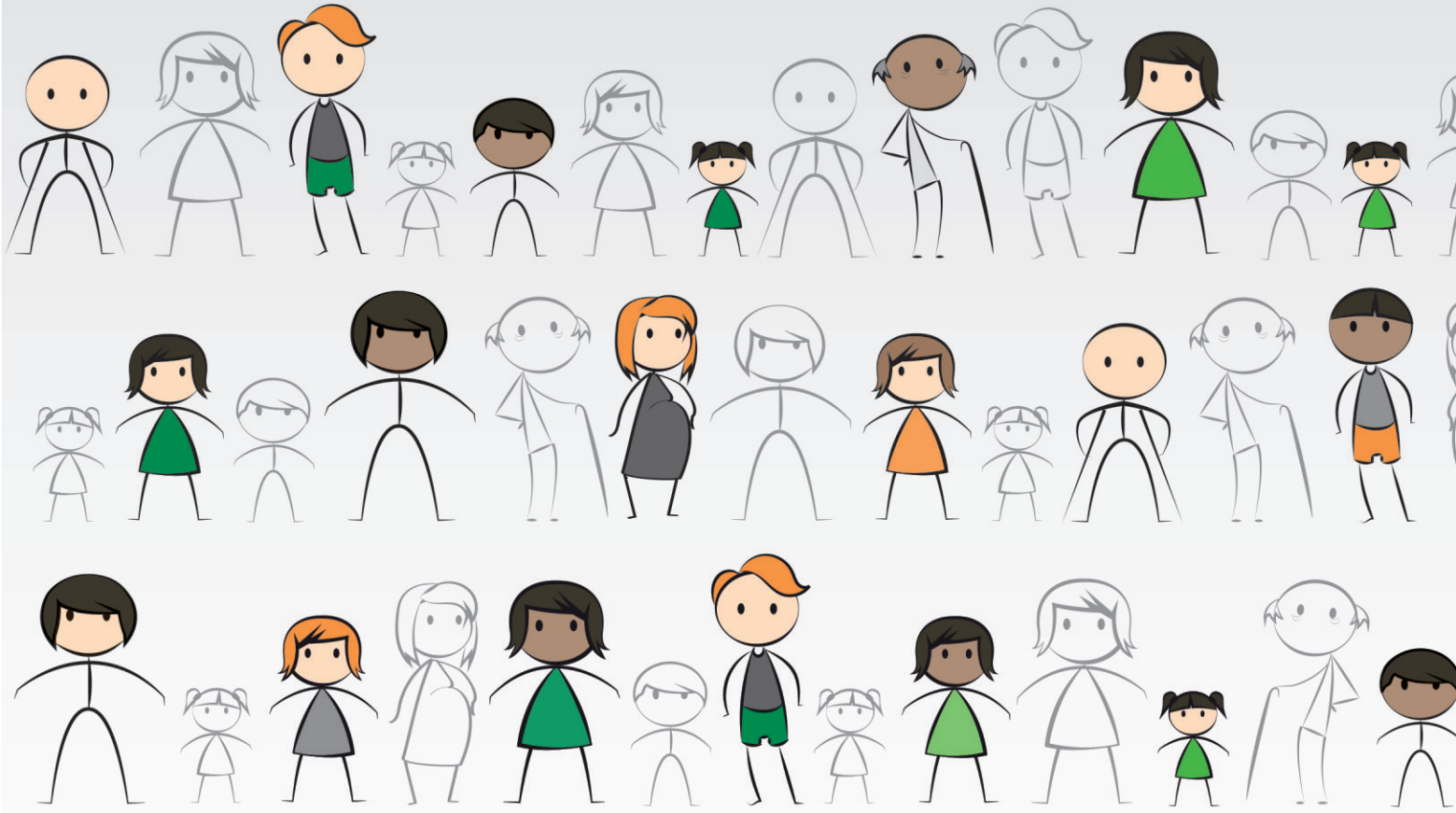

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TABLE 1

MR format	Objective	Formulation technology
Gastro-retention	• Delay gastric emptying from the stomach to deliver the drug over a prolonged timeframe to the upper GI tract when an absorption window exists.	Swellable, raft, floating, and bioadhesive systems
Gastric bypass	• Prevent release of the drug in the stomach and/or upper gastrointestinal tract • Overcome gastric irritation or instability of the drug	Enteric coated tablets or capsules
Sustained or extended release	• Extend the *in vivo* release profile of the drug or enable 1-2x daily dosing	Matrix tablets, coated tablets, or multiparticulates
Delayed release	• Release the drug at or near the intended site of absorption or action such as upper small intestine or colon • Deliver time, pH, and/or microbially triggered release	Tablets, capsules, or multiparticulates
Biphasic release	• Eliminate the need for repeat dosing • Provide rapid therapeutic effect from an immediate release layer and extended dosing via a sustained release layer	Bilayer tablets or multiparticulates
Pulsatile release	• Drug release as a pulse after a predetermined lag time — designed according to the body's circadian rhythm • Beneficial release mechanisms for time-dependent dosing or for drugs that undergo first-pass metabolism	Bilayer tablets or multiparticulates

A selection of MR formats, their behaviors, and the technologies they represent.

in the GI tract, and intestinal motility) can impact a product's performance as it transitions through the intestine. Given these variables, being sure the formulation performs *in vivo* as it did *in vitro* can be challenging. A good CDMO will help developers find the best approach and select a technology to achieve the desired performance.

The Rocky Transition From Lab to Human

What is the best way to predict a formulation's clinical performance? Ultimately, how an MR delivery system will perform in humans is unknown until clinical PK data becomes available, no matter what the *in vitro* and preclinical data indicated. Successful performance depends on an interplay between the drug molecule, the formulation, and the gastrointestinal environment. Despite their long-term, widespread use for this purpose, *in vitro* and preclinical studies cannot always be relied upon to predict how formulations will perform in humans.[2,3]

There are many reasons why animal studies are not necessarily predictive of how a drug will behave when administered to humans. The pHs in the various segments of animals' GI tracts differ from those in the corresponding segments in humans. Animals' stomachs exert different peristaltic wave forces and have different gastric-emptying rates as well, so diffusion rates, release rates, and PK profiles are not always representative. The best model for a human is a human.

A traditional clinical investigation for developing an MR system would be to test 2-3 fixed-formulation prototypes, such as a slow formulation, a fast formulation, and perhaps one in between based on *in vitro* and preclinical data, and hope one achieves the desired PK profile. But if these combinations miss the target PK profile, an

additional time-consuming development cycle will be required, incurring a delay of 12-18 months and additional outsourcing costs of $1.5-$2.5 million. In contrast, using a design space concept will produce the required PK profile efficiently, in a single development cycle.

THE DESIGN SPACE STUDY MEETS REAL-TIME MANUFACTURING

The most obvious question when planning to develop an MR dosage form is: What is the starting composition and dose? *In vitro* dissolution studies are an invaluable tool to inform formulation development. However, there is considerable uncertainty as to whether a fixed formulation that achieves the desired release rate *in vitro* will also deliver the required performance in humans. If the starting formulation misses the mark completely, a second clinical study with an adjusted starting formulation will be required, leading to escalating costs and time delays. Fortunately, by implementing adaptive design strategies such as the design space (DS) approach, developers can mitigate this risk.

The Design Space Concept

The International Conference on Harmonisation (ICH) and FDA define DS as:

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality (ICH Q8).[4]

These regulatory definitions are focused on late-stage development, and the importance of defining a "safe space" within which changes in product and process parameters will not affect clinical performance. The same principles, however, can be applied to early development to maximize the potential to optimize formulations within a single clinical study. Rather than specifying exact values for API and excipient contents, developers can set ranges for these critical-to-performance parameters in the regulatory application. By varying the quantitative levels of these components during clinical conduct, product performance can be influenced and the formulation optimized based on human data. These DS ranges represent acceptable, safe limits based on toxicology studies and PK data collected earlier. Product quality is ensured through inclusion of technical batch data in regulatory documentation. An approval of a complete DS gives developers leeway to adjust formulations as needed within the pre-approved ranges during study conduct. This freedom mitigates risk in MR formulations by giving the Phase I clinical trial process the best possible chance of achieving the desired drug delivery profile – without the need for repeat development cycles.

How Design Space Maximizes Trial Flexibility

The DS concept can be applied to any formulation, drug product, or dosage form. The goal in MR formulations is to address all the adjustable, critical-to-performance parameters that can influence release rate and PK profile. While mapping two variables is common, it is possible to define the DS for as many as are relevant.[5] For example, any of these following parameters could be considered as part of the DS:

- API dose/concentration
- Functional excipient content
- Drug:polymers ratio
- Surface area volume ratio
- Coating composition/thickness

FIGURE 1

Formulation design space. Initial data will be generated using the corner points. The large, square diagram represents the use of two variables, but other numbers of variables may be considered simultaneously. For example, from left to right, the small diagrams represent 1, 2 interdependent, 2, and 3 variables.

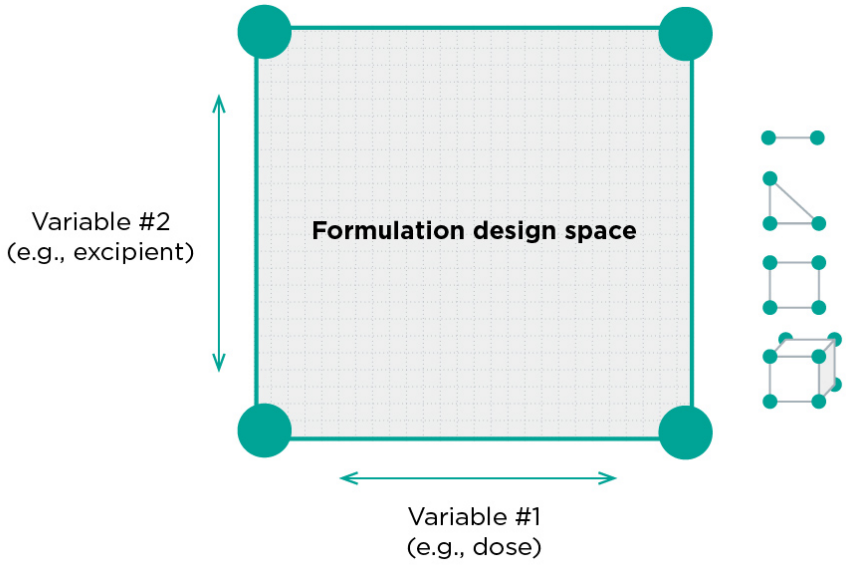
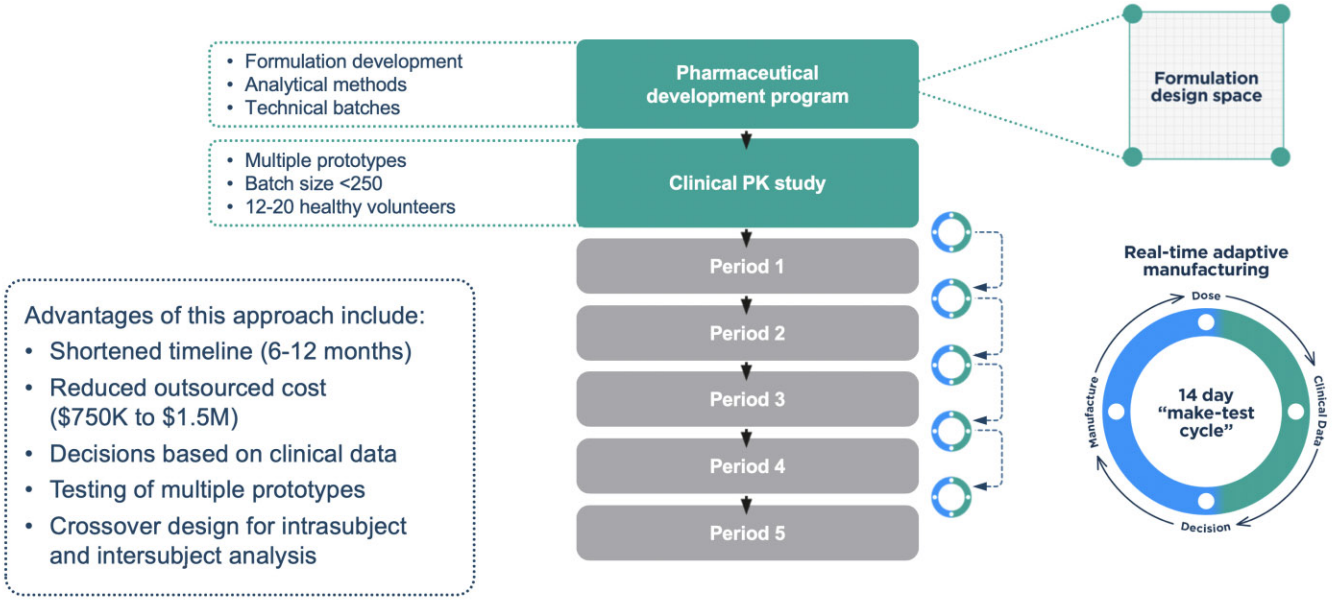


FIGURE 2



Design-space-based development followed by real-time adaptive manufacturing with a 14-day make-test cycle, for example, sharply cuts the overall trial time by shrinking the intervals between test periods.

Extremes of release rate can be developed *in vitro*, and the corresponding critical parameter values may be used as the minimum and maximum values to define the DS – the corner points (Figure 1).

Any formulation within this map may be manufactured and dosed without any regulatory amendment or notification. As clinical results develop, trial medications will be adjusted accordingly to optimize the drug-release pattern and increase or decrease the dose as required.

How CRO & CDMO Functional Integration Enables Real-Time Manufacturing & Shrinks Timelines

The flexibility a DS concept affords is only beneficial to the extent that manufacturing can keep pace with the clinical trial dosing modifications. Seamlessly integrating a manufacturing facility with the clinical testing organization running the study can shrink the time between decision points and restart the trial with the next iteration of drug product (Figure 2).

Overall benefits of applying this rapid formulation development and clinical testing approach on demand, as products evolve in the development cycle include the following:

- Timeline shortened by more than 6 months
- Cost of outsourcing reduced by $750,000-$1.5 million
- Formulation selected based on clinical data
- Minimal API waste
- Seamless optimization of formulations for scale-up to commercial manufacturing

Pharmaceutical development teams from more than 50 pharmaceutical and biotechnology companies worldwide have completed more than 100 programs like this while developing optimized MR formulations for small molecule drugs across all major therapeutic areas.

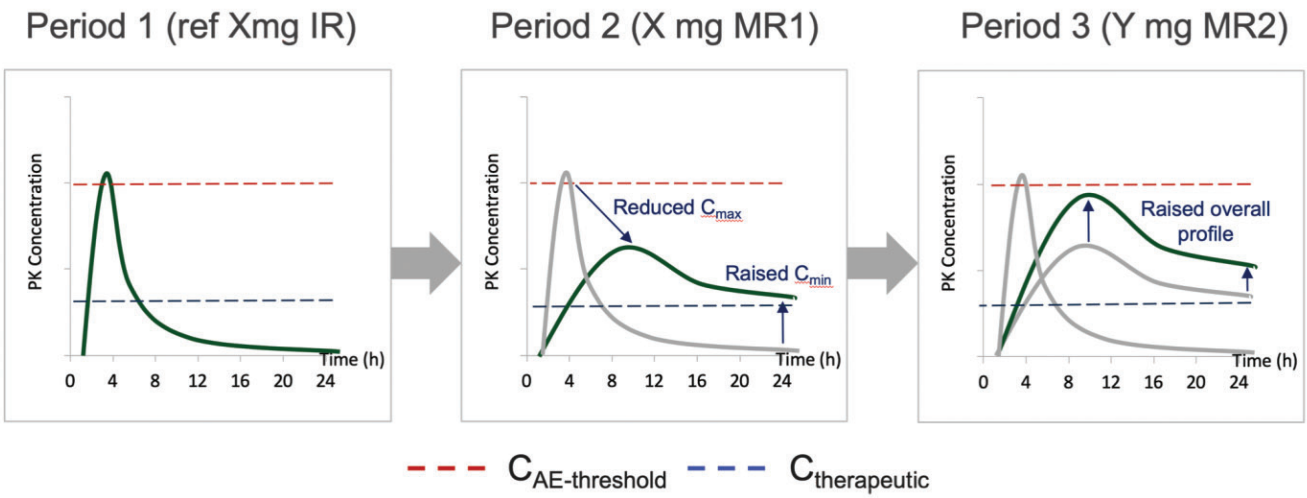
CASE STUDY

Development & Optimization of an MR Formulation Without Relying on Predictive Laboratory or Preclinical Models

A mid-size pharmaceutical company wanted to develop a once-daily format for an existing immediate-release (IR) formulation. An attempt to develop an MR matrix tablet formulation by traditional methods failed to achieve the desired PK profile, and resulted in C_{max} related adverse events and sub-optimal therapeutic levels. The company enlisted an innovative CDMO's help to develop the required formulation using a DS approach with dose and release rate (as determined by HPMC content) as the key variables.

During the development phase, technical batches with 14-day stability data were produced for the four corners of the design space — the extremes of each variable. These batches were fully characterized using qualified analytical methods in

FIGURE 3



PK profile progression during single-dose MR prototype selection. Each new formulation is modified and comes closer to the desired profile. Period 1 reflects the reference IR formulation. C is concentration, AE is adverse events, and AUC24 is area under the curve over 24 hours.

support of the regulatory filing.

Once the application was approved, the clinical PK study in healthy volunteers began, with an initial IR reference period followed by sequential, fasted trials. The initial prototype formulation, within the design space, was determined by PK modelling. Each set of emerging PK data drove selection of the next MR prototype, which was manufactured, quality control tested, and released for dosing without additional approval or stability studies, just days before the next test period. This cycle ended when the PK profile fell within the desired range. Results are shown in Figure 3. One final round was conducted with fed study patients to test the food effect on the PK of the final formulation. This approach identified a tablet prototype with C_{max} < 40% and C24 > 200% relative to the IR tablet in 7 months.

Through the integration of formulation design space, real-time GMP manufacturing, and an iterative sequential pharmacokinetic study, an HPMC matrix tablet with desired PK characteristics was developed. Human PK data guided formulation composition, eliminating the need to rely on surrogate, non-predictive laboratory or preclinical data.

OPERATIONAL CHALLENGES: MEETING REGULATORY EXPECTATIONS

To succeed in applying design space concepts to de-risk and expedite clinical trials, scientific and regulatory expertise must go hand in hand. In-depth understanding of the evolving clinical trial regulatory environment will ensure the preparation of high-quality IND applications and institutional review board (IRB) submissions that will satisfy regulatory authorities.

To approve a DS concept, authorities will first need to know how it is mapped: which critical material, process parameters, and/or product quality attributes are the intended variables. The justification package must then provide the following:

- Assurance that systemic exposure of the drug will not exceed that previously demonstrated to be safe and tolerated in humans
- Well-established evidence of safety for all excipients
- Well-established relationship between excipient variables (e.g., molecular weight or levels) and release rate
- Logic of the design space extremes – for example, is the API dose range reasonable based on a sufficient body of supporting information?
  -The minimum (therapeutic efficacy)
  -The maximum (toxicity/adverse events data)
- Evidence of product quality and stability within the DS to support the duration between manufacture and dosing

To ensure the strongest possible dossier, a collaborative relationship with the IRB is extremely helpful. A CDMO with

regulatory personnel who routinely present DS concepts is most likely to achieve a seamless submission and approval process for this type of Phase I clinical trial application - provided that the science and production are impeccable. Successful 14-day make-test cycles demand operational speed and excellence with strong project leadership to integrate clinical and manufacturing activities while managing logistics.

CONCLUSION

Developing MR formulations that fit a target PK profile is far from simple, with many potential delivery technologies to select from and much uncertainty regarding performance in a physiological system. Use of a DS concept saves time and removes uncertainty surrounding achieving the clinical performance of a formulation. With the flexibility to vary the formulation as the clinical trial progresses, a DS concept diminishes risk by increasing the likelihood that the desired PK profile will be achieved relatively quickly, without the need for additional regulatory approval.

An integrated operational set-up allows developers to take maximal advantage of DS concepts through the interplay of manufacturing and clinical testing. Through an iterative make-test cycle, a series of prototypes are rapidly reformulated based on emerging clinical data until the desired performance is achieved. This approach accelerates timelines and greatly diminishes the risk of failing to achieve the desired product.

Advantages of combining a DS approach with real-time, on-demand manufacturing include the following:

- Faster drug development and formulation optimization
- Lower R&D costs
- Lower risk
- Science-based product development
- Seamless transition to Phase II drug product and commercial manufacturing

Enlisting help from a partner with extensive experience in design space, the regulatory expertise to gain approval for them, and the operational capacity to provide real-time manufacturing will ensure successful implementation. ◆

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BIOGRAPHY

Andy Lewis, PhD, is Vice President, Pharmaceutical Sciences at Quotient Sciences, leading a team of 120 scientists who work on formulation development, clinical manufacturing, and pharmaceutical analysis for clients' drug product programs. Previously, he was Director of Novel Drug Delivery Technologies at Ipsen (France), where he had global responsibility for product development, utilizing novel formulation technologies or drug delivery devices. He has also assisted in the development and growth of two venture capital funded start-ups, RegenTec and Critical Pharmaceuticals. There he led the development and commercialization of novel technologies in the fields of tissue engineering and drug delivery, taking them from concept into clinical development. Dr. Lewis has a particular interest in overcoming drug delivery challenges, including sustained release and transmucosal delivery of proteins and peptides, and he has filed a number of patents. He is a member of the Academy of Pharmaceutical Scientists of Great Britain; has served for 4 years as the Director-at-Large of the Controlled Release Society (CRS); and is a committee member on the Board of Scientific Advisors.

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ON-BODY DELIVERY SYSTEMS

Analysis & Simulation of Injection Volume Accuracy

By: Christian Riva, MS

INTRODUCTION

In the past several years, in parallel with the increasing development of new molecules, there has been a steadily rising attention among the world's largest pharma companies to subcutaneous drug delivery devices that can help patients safely self-adhere to their therapy plans.

Of particular interest is replacing legacy autoinjectors with wearable, prefilled on-body delivery systems (OBDS), which represent a revolution in the field of drug delivery. Ease of use and disposability are key factors that are convincing even more players in the market to invest in the development of such devices.

Despite the fact these on-body devices are delivering a subcutaneous bolus to the patient, the accuracy and delivery rate of the drug volume are two of the major performance requirements the system must fulfill.

While injection volume and rate accuracy may be specified for a generic system, the ability of this new wearable system to accurately deliver "labelled" quantity at the desired delivery rate or within the desired time can significantly change the system architecture. Baseline for delivery accuracy inputs typically comes from three primary sources:

– **Market-Driven:** understand similar combination systems (predicate devices) already present on the market or approved by regulatory bodies and their variances

– **Therapy-Driven:** understand the allowable variance from a physiological perspective

– **Standards-Driven:** understand the allowable variance guided by the chosen applicable standards.

It is therefore essential to fully define the system needs specific to these inputs from an early development stage, when most of the strategic decisions affecting product development are made. In this review, we will explore key design considerations that impact the volume or dose accuracy.

CONSTRAINTS GIVEN BY NORMATIVE & PRODUCT STANDARDS

Although the adherence to product standards is not mandatory, the development of drug delivery systems (Pen Injectors, Auto Injectors, OBDS, Infusion Volumetric Pumps) is usually driven by the following set of standards:

– ISO11608-1:2014 Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems

– United States Pharmacopeia USP <905> Uniformity of Dosage Units

– IEC60601-2-24:2012 Medical electrical equipment - Part 2-24: Particular requirements for the basic safety and essential performance of infusion pumps and controllers

– ISO11608-6 (DRAFT under development – stage 30) Needle-based injection systems for medical use – Part 6: On-body delivery systems. This last is a new part (still under evaluation) for the OBDS that refers to Part 1 and is related to Injection Volume Accuracy

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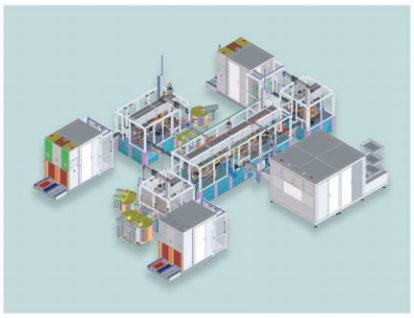

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Each of these standards establishes clear requirements (depending on the device classification) and test methodologies to assess the capability of a system to accurately deliver the prescribed volume to the user or patient.

DIFFERENCES BETWEEN BOLUS & MULTI-DOSE AUTO INJECTORS

When it comes to dose accuracy, single-dose OBDS are in general, asked to deliver "at least" the value that is declared on the product label, while reusable multi-dose autoinjectors will generally guarantee a min-MAX accuracy for each single delivered dose.

Technically speaking, for an OBDS that aims to deliver the entire content of the primary container, the variability of the volume injected mainly depends on its geometric characteristics and on air trapped inside the primary container. For reusable autoinjectors, other factors like priming, ability to accurately control the primary container stopper movement, and system volumetric compliance all contribute to the overall system performance.

Hereafter, a more complete evaluation of the Injection Volume Accuracy tailored on OBDS is reported to show through a simplified case study, the effects given by both air trapped and hold-up volume of the primary container.

VARIABLES & PARAMETERS AFFECTING DOSE ACCURACY

In general, the dose accuracy or injection volume accuracy for systems aimed to deliver the full dose of the primary container can be calculated according to the following equation:

Equation 1.

$$V_{injected}|_{t=EoD} = V_{filled}|_{t=0} - V_{residual}|_{t=EoD}$$

where:

$V_{injected}\,|_{\,t=EoD}$ represents the volume of drug delivered to the patient, once the injection has been completed (EoD = End Of Dose or Injection).

$V_{filled}\,|_{\,t=0}$ represents the volume of drug inside the primary container. This value is established by requirement and only affected by the natural variance of the fill/finish process.

$V_{residual}\,|_{\,t=EoD}$ represents the volume of drug not delivered to the patient during the injection but that remains/accumulates in the drug delivery system once the injection is completed.

This last parameter is particularly interesting because it is mainly affected by:

– Geometric dimensional variability of the fluid path, caused by the natural manufacturing tolerances of the individual components part of it (e.g., tubing, needles, cannulas, manifolds, etc)

– Geometric dimensional variability of the part of the primary container between the septum and the stopper (typically the cartridge/PFS shoulder), so-called "container hold-up" volume

– The presence and the volume of the air bubble trapped in the primary container during the fill/finish process.

The air bubble, in fact, plays a major role in the calculation of the injection volume accuracy. In the two extreme cases, it can be acknowledged that:

If the primary container doesn't contain any air (but only drug) or it is oriented in a way that the air is immediately delivered as part of the drug (as can happen during a priming process), at the end of injection, both the fluid path and the primary container volume will contain only the drug. This residual volume of drug, not delivered to the patient and defined as overall "Hold-Up Volume," should be taken into consideration and compensated for by over-filling. This mitigation guarantees to avoid systematic under-doses, but at the same time increases the drug-related cost.

Under this condition, the amount of drug that the system can deliver to the patient represents the Minimum Possible Dose:

If the primary container contains a significant air bubble or it is oriented to let the air stay in the system (adherent to the stopper), at the end of injection, both the fluid path and the primary container hold-up volume will contain a percentage of air that depends upon the relative ratio within the overall system dead volume. If the volume of the air trapped is nominally greater than the overall system hold-up volume, all the content of the primary container is delivered to the patient. Considering that the primary container needs to be overfilled to compensate for the hold-up volume, this second condition represents the Maximum Possible Dose that the system can deliver to a patient.

To give a rough idea of the typical size of the air bubble trapped in cartridges according to a standard fill/finish process, it is reasonable to consider the stopper positioned at a distance of 0.4/0.7 mm from the drug level, having therefore a volume

of air into the primary container of about 45-80 µl (for a 3 ml, 12 mm ID primary container). Lower values can be achieved with vacuum stoppering technologies that allow minimized volume of air trapped during the sealing of the primary container after filling.

These numbers are typical for cartridges with standard stoppers. In prefilled syringes (PFS) the "hold-up volume" is significantly smaller, reaching values in the range of a few microliters.

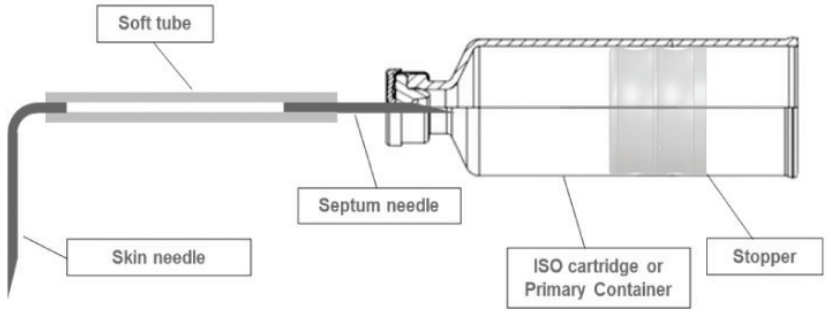
It is possible to numerically model the previously listed variables and quantify their effect on the overall volume injection accuracy. The numerical simulations obtained computing all the inputs and variables involved can be either used to guide the design process of the system or to verify the compliance of an existing system with the given requirements of injection volume accuracy.

CASE STUDY: MODELLING & CALCULATION METHODOLOGY FOR WEARABLE OBDS

Hereafter, the main outcome of a numerical simulation of injection volume accuracy exercised on a wearable patch injector or OBDS is reported. The simulation was planned and executed to guide the design process of the entire system and verify the compliance to a given requirement of injection volume accuracy.

Simplifying, the object of the simulation (therefore the core of an OBDS) can be represented by the system in Figure 1, where an ISO13926- compliant 3.0 ml (12 mm ID) glass cartridge is connected to a 25 G needle (so-called "Septum Needle"), to a 0.5 mm ID soft tube and to a 27 G needle (so-called "Skin Needle"). The other end of the system is delimited by the primary container stopper.

FIGURE 1



System analyzed in the case study. This represents the example of the core assembly for an OBD Device.

The main assumption behind the numerical evaluation of the dose accuracy is that the system is equipped with enough energy to guarantee that the primary container stopper can reach the mechanical End-of-Travel (e.g., cartridge shoulder) considering all the tolerances affecting the system.

To do that, it is mandatory to design the subsystem responsible to move the stopper (extrusion or drive subsystem) computing all the forces that it must overcome to deliver a given value of drug in a given time interval. This is particularly important if the system (or, as often happens, the platform) is designated to inject multiple drugs with a wide range of viscosities.

Equation 2.

$$F_{drive}\left(x(t),\ \frac{dx(t)}{dt}\right) = F_{drug}\left(x(t),\ \frac{dx(t)}{dt}\right) + F_{friction}$$

The resolution of the time-dependent differential equation allows one to properly compute for:

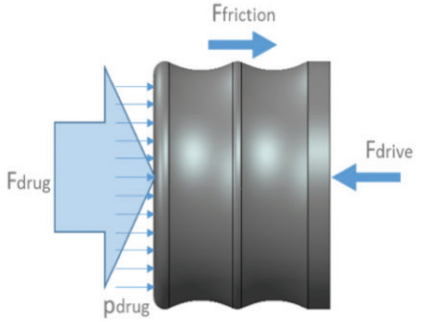
- all the pressure drops/losses inside the fluid path
- the friction (static and dynamic) offered by the sliding of the stopper along the primary container barrel
- the mechanical characteristics of the drive subsystem, as a function of the energy source it uses (e.g., mechanical spring, electromechanical actuator, gas cartridge, etc).

This process allows for the design of systems where systematic under-doses due to incomplete travel of the primary container stopper never happen; and for those cases caused by single fault events, monitoring functions shall be in any case added to the device as risk control measures.

At this point, the injection volume accuracy can be calculated by the resolution of Equation 1. In order to have a more realistic representation of the variability of the results, a Monte Carlo statistical approach can be used.

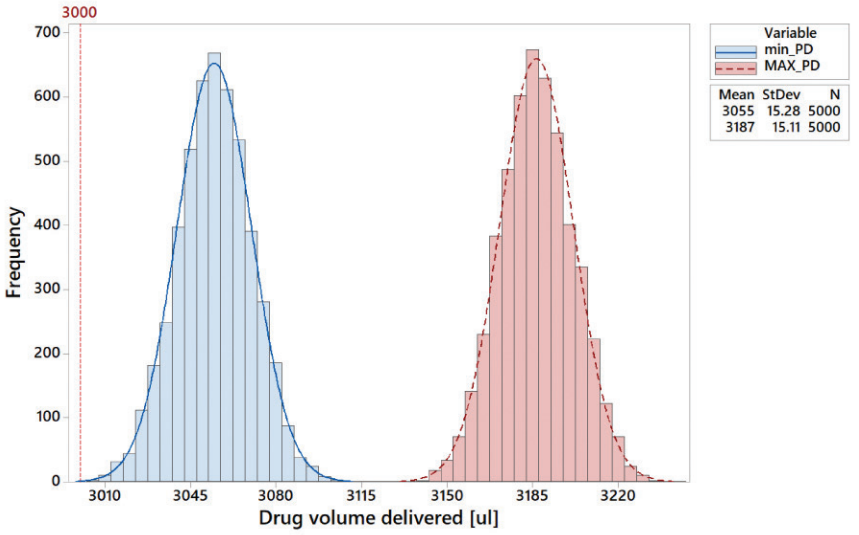
With this approach, it is possible to generate a set of results (for the volume of

FIGURE 2



Dynamic balance of forces (loop) on a cartridge stopper.

FIGURE 3



Distributions obtained by the Monte Carlo simulations for the volume of drug delivered to the patient (sample size: 5000).

drug delivered to the patient) corresponding to a random variation of the input variables within their allowed tolerance ranges. This enables a statistical distribution from which statistical indicators (average and variance) can be inferred (see equation 3 below).

Equation 3.

$$V_{injected}\big|_{t=EoD} = N(\mu, \sigma)$$

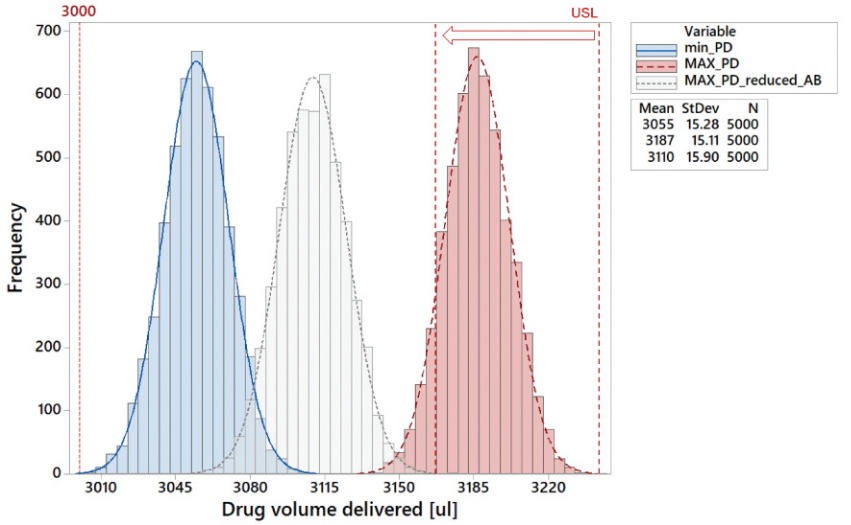
The plot in Figure 3 shows the result of a simulation (run on a sample size of 5000 simulated devices) for $V_{injected}$. The blue distribution represents the minimum Possible Dose (min_PD) that can be delivered to the patient. The left tail is positioned just at the right of the amount to be delivered by requirement (3 ml) with an average slightly moved to the right to include the natural variability of the hold-up volume and of the filling process. In the event that an air bubble greater than or equal to the hold-up volume is trapped, in the worst case, the quantity of drug delivered can be represented by the red distribution. The distance that characterizes this distribution from the previous represents the offset generated by the overfilling. The bigger the hold-up volume, the greater the overfilling required is to meet the dose requirement in case all the air is immediately injected to the patient at the start of the therapy. On the other hand, in case the air is able to expel all the liquid from the primary container and the fluid path, a larger dose results delivered to the patient.

The difference between the right tail of the Maximum Possible Dose (MAX_PD) and the left tail of the minimum Possible Dose defines the tolerance range (USL-LSL) for the injection volume accuracy.

By reducing the volume of the air bubble (eg, by use of vacuum stoppering technologies in fill/finish) it is possible to observe a movement of the Maximum Possible Dose distribution toward the Minimum Possible Dose distribution, because the probability of having liquid into the fluid path increases. When $V_{AirBubble} \rightarrow 0$, the Maximum Possible Dose Distribution tends to overlap to the Minimum Possible Dose distribution, narrowing the tolerance window for the injection volume accuracy.

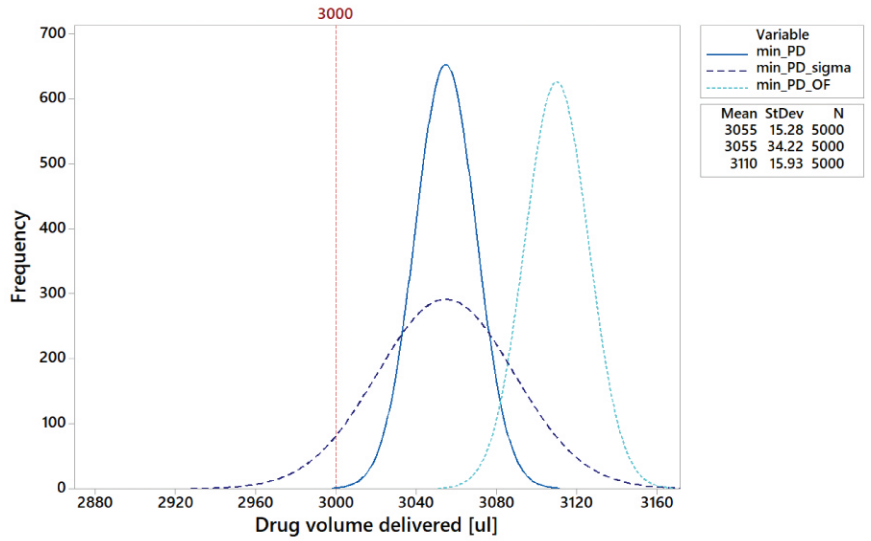
This dual representation of the aforementioned distributions can also be associated with the device orientation that cannot be modelled and randomized as can the other contributors to the equations. In the first case (blue distribution), the orientation allows the air to exit the system immediately after the fluid path opening. At the other extreme (red distribution), the orientation will play the opposite role: the air

FIGURE 4



Effect produced by the decrease of the air bubble volume in the primary container: the red distribution tends to move toward the blue, tightening the tolerance range.

FIGURE 5



Effects produced on the drug delivery profile in function of: natural tolerances of the hold-up volume (min_PD_sigma) and drug overfilled (min_PD_OF) into the Primary Container.

stays inside the system until the end of delivery, causing the extrusion of all of the drug initially contained in the primary container.

Once the effect of the air bubble is captured and its volumetric value established/optimized, the numerical model can be used to optimize the system geometries to best match the target accuracy window, taking into account the typical tolerances of the components' manufacturing processes.

The plot shown in Figure 5 qualitatively highlights how the geometric tolerances of the fluid path components and over-filling are modifying the volume of $V_{injected}$:

CONCLUSIONS

The aforementioned methodology demonstrates that it is possible to have a realistic prediction of the injection volume accuracy of a drug delivery system, even in an early stage of product development, when only a high-level product architecture is available.

The statistical numerical model developed, which includes the realistic variation of all the variables involved, allows one to:

– Evaluate the performance of a system against a given requirement and hence change or reject it

– Support the design process to optimize the system to reach the desired performance level

– Through sensitivity analyses, identify the most critical parameters that may call for particular attention during manufacturing

– Accurately estimate the system dead volume and its natural variance, which is directly linked to the volume of drug to be over-filled and therefore directly linked to cost

The aforementioned approach is particularly important for systems and platforms that have an intrinsic and non-negligible hold-up volume. For systems that use cartridges or custom solutions for the primary container, the presence of the air trapped is significantly increasing the variability of the actual delivery profiles, hence demanding a wider tolerance window for the delivery.

PFS (prefilled syringes) are less affected by the presence of the air bubble. Considering the almost negligible hold-up volume, virtually all of the drug is delivered in a single dose; this leads to narrower tolerance intervals for injection volume accuracy and reduces the need and the extent of the over-filling. ◆

BIOGRAPHY

Christian Riva is a Senior Systems Engineer at Flex, a global company providing design, engineering, manufacturing, supply chain, and logistics to companies across industries, including medical devices. He manages the development lifecycle for drug delivery, on-body delivery systems, wound management, and wearable diagnostics. He began working at Flex in 2010 as a Mechanical Design Engineer for In-Vitro Diagnostic Medical Devices, and later, electromechanical Drug Delivery Devices. He earned his MS in Mechanical Engineering from Politecnico di Milano Tech University in Milan, Italy.

IMMUNOTHERAPY

A New Direction for CAR-T Cell Immunotherapy

By: David Gilham, PhD

BACKGROUND

Despite advances in radiotherapy, chemotherapy, and surgery, many cancer patients relapse with little prospect of effective treatment for disease that, in many cases, has developed resistance to standard therapy. Immunotherapy, a new paradigm of therapy exploiting the power of the immune system, is now providing treatment options that may offer hope to at least some of these patients with advanced cancer.

Monoclonal antibodies have driven the first wave of modern immunotherapies. Immune checkpoints are included in this class. They work by releasing the power of the immune system and, more specifically, T-cells that are the key immune effector cells that can kill cancer cells. Now the next wave of immunotherapies is focusing more on exploiting the immune effector cells directly rather than indirectly releasing their activity through an antibody. To this end, chimeric antigen receptor (CAR) technology directly exploits the T-cell by extracting them from the patient, engineering them with a tumor targeting receptor, growing to large numbers, then returning the CAR-T cells back to the patient by an infusion into a vein. The infused CAR-T cells can then travel around the body seeking out cancer cells that they can kill. Unlike an antibody, these CAR-T cells are a living drug and can actively migrate into tumor tissue, multiply, and potentially provide a long-term antitumor effect.

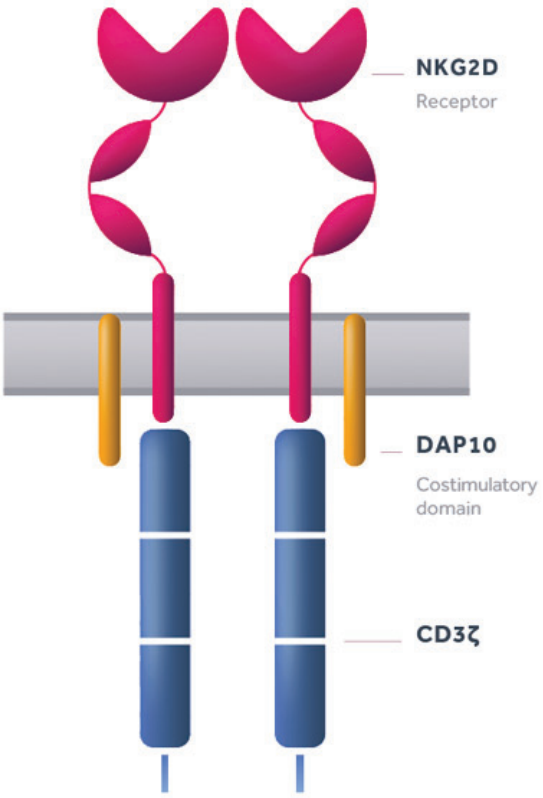
CAR-T cell therapy has exploded onto the clinical scene due to a specific CAR that can target certain leukemias and lymphomas. The spectacular clinical responses seen in this first CAR-T approach has led to the rapid licensing of CD19 CAR-T cell therapy that is a breakthrough for patients with previously treatment-resistant relapsed leukemia. This has stimulated the field to explore the therapy in cancers that are harder to treat, such as solid tumors.

Celyad, a clinical-stage biopharmaceutical company, is at the front of the next wave of CAR-T cell therapies using a targeted approach against both blood and solid cancers. In parallel, Celyad is exploiting technology that can move CAR-T from the patient specific area (autologous CAR-T) to an "off-the-shelf" approach based upon banks of CAR-T cells produced from healthy individuals that can be used to treat many patients (allogeneic CAR-T cell therapy).

INTRODUCTION

CAR-T cell therapy, which is an elegant approach to cancer treatment that has potential to drive patient-led medicine forward, involves modifying specific immune cells collected from a patient that can be used to target and better destroy cancer cells. Overall,

FIGURE 1



Schematic of CYAD-01

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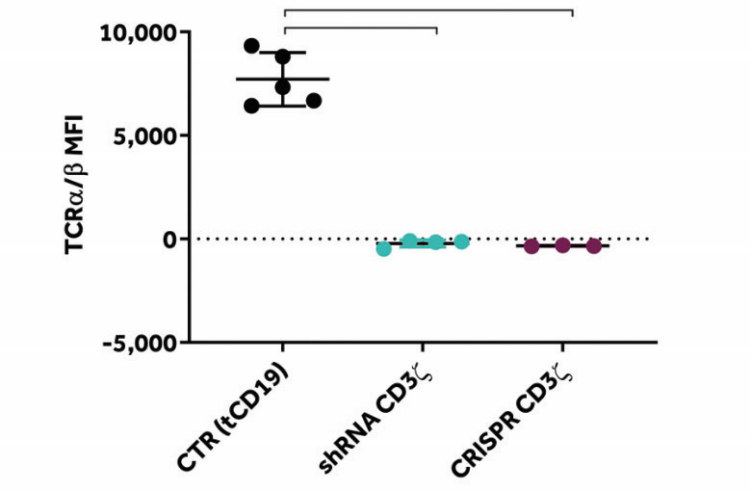
more than 200 clinical trials have been conducted or are in progress on CAR-T therapies, the majority of which have focused on the treatment of blood cancers.[1] The most frequently targeted blood cancer-specific antigen is CD19, a cell surface protein commonly found on cancerous cells derived from B cells, which has been studied in more than 70% of hematological malignancies targeted trials thus far.[1] The Federal Drug Administration (FDA) has currently approved the use of only two CAR-T therapies, both of which aim to treat relapsed/refractory B-cell malignancies by targeting CD19. Unfortunately, non B-cell hematological malignancies such as acute myeloid leukemia (AML) which has a dismal 26.9% 5-year survival rate, is not applicable for CD19-targeted CAR-T therapy as these cancerous cells do not possess the CD19 target protein.[2] Of note, there has yet to be an approved CAR-T therapy that can be used outside of the B cell malignancy area.

For CAR-T, T-cells are transduced with viral or non-viral vectors engineered to generate CAR-T cells. The vector system carries a gene that encodes the CAR which when integrated into the T-cell produces the CAR protein that then goes to the surface of the T-cell. The CAR protein is a fusion composed of a cancer cell recognizing domain (antigen-binding) and a T-cell activating receptor domain. Hence, upon successful engagement of the antigen-binding domain with its target on a tumor cell (such as CD19 on a B cell), the T-cell activating domain drives the effector function, resulting in the direct killing of the tumor cell. After killing its prey, the CAR-T cell then moves on searching for more tumor targets. This underlies the premise of the CAR-T as a "living drug," where the T-cell is able to circulate, kill cancer cells, and move on looking for more cancer cells to kill.

FIGURE 2



Celyad's shRNA platform shows similar reduced TCR expression than CRISPR/Cas9

Since the first description of the receptor in the late 1980s, CARs have undergone serial developments primarily focused upon optimizing the T-cell activating domain.[3,4] Today, the second-generation CAR is the most common in use and the configuration that has been successfully licensed involves two signal generating domains that can drive the full activation of the T-cell and strong cancer cell killing.

Given this development, the current paradigm for CAR-T cell therapy involves using T-cells from the patient that are modified and returned to the same patient – so called "autologous therapy." The clear benefit of this approach is that the T-cells are from "self" and thus able to be re-infused into the patient with little issue. The success of this approach is reflected in the clinical products Kymriah and Yescarta.

Despite the success of these products, there are two main downsides. The first is time needed to generate the CAR-T cells (usually in the region of weeks), which is particularly critical for patients with acute, rapidly developing disease. The second is the inherent variability associated with using a patient-specific starting material, which consequently leads to variation in characteristics of the end-product.

A newer approach that may circumvent these specific issues is allogeneic CAR-T cell therapy, where the source of T-cells used to generate the CAR-T product is derived from a healthy donor. The intention here is to generate these cells ahead of time and bank them. These CAR-T cells can then be released as and when needed for the patient without the lag associated with the autologous product. Moreover, the use of healthy donors means there is far greater consistency in the starting course of cells. Whilst still at the earliest stages of development, the ability to generate multiple patient lots within a bank would most likely be associated with a reduced manufacturing cost as compared to that to produce a patient-specific just-in-time product.

However, allogeneic CAR-T cell therapy is not without its challenges, which relate to the use of cells that are "non-self." The first is that a host versus graft (HvG) response may occur resulting in rejection of infused T-cells because these cells will be recognized as foreign by the patient's own immune system, thereby rendering the entire treatment process futile. Second, a complication known as graft versus host

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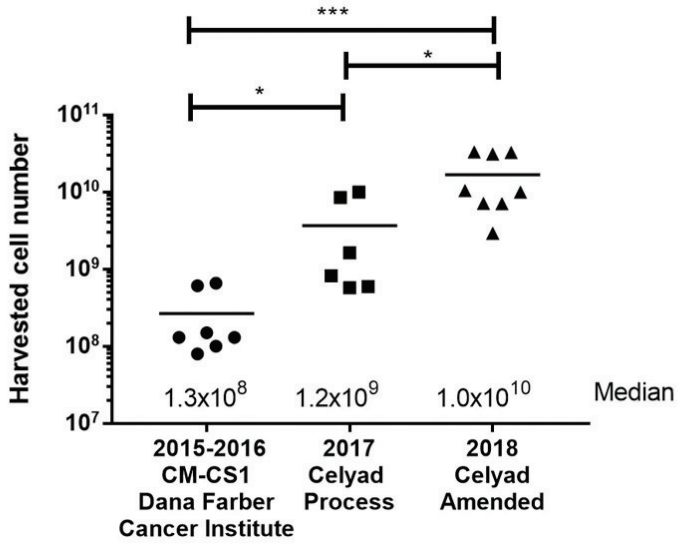
FIGURE 3



Optimized process leads to substantial log increase in cell yield (taken from Celyad-RnD Day PPT)

disease (GvHD) in which the donated T-cells recognize the recipient (patient) cells as foreign, resulting in the T-cells attacking healthy tissue.

Both events are clearly undesirable for the use of allogeneic CAR-T cell therapy. However, solutions are now in place. To control the HvG response, a chemotherapy regimen that transiently depletes the patient's immune system (known as pre-conditioning chemotherapy) is given to the patients shortly before infusion of the allogeneic CAR-T cells. This effectively provides a window of opportunity for the CAR-T cells to freely move around the patient seeking out cancer cells. The effects of the chemotherapy wear off around 7 to 14 days later at which point the patient's immune system regenerates and would likely then eliminate the therapeutic CAR-T cells. This means the allogeneic CAR-T cells have a limited time to do their anti-tumor work but, on the beneficial side, it is likely that these cells will therefore persist for only a short time, meaning the treatment will be effectively self-limiting.

Dealing with the GvHD response is trickier. All T-cells possess a specific protein structure called the T-cell receptor that defines the T-cell. This receptor can recognize specific molecules present on most of our cells (called human leukocyte antigen or HLA). In the allogeneic situation, the T-cell receptor on the donor allogeneic CAR-T cells recognize the HLA on the patient's tissues as foreign and instructs the T-cells to attack leading to GvHD disease. Due to molecular engineering, there are now options that can interfere with or eliminate the T-cell receptor on allogeneic CAR-T cells, thereby preventing the onset of GvHD and allowing tumor-specific killing through the CAR.

CELYAD'S CAR-T THERAPIES IN CLINICAL DEVELOPMENT

Celyad's predominant focus is on exploiting CAR-T cell therapy through a novel target-binding domain called NKG2D (Figure 1). This protein is attractive because it can bind up to eight different targets (MHC class I chain-related proteins A and B [MICA/MICB] and UL-1 to 6 binding proteins [ULBP]) which are over-expressed on at least 80% of tumors, yet are absent or minimally expressed on normal healthy tissue.

Many binding domains used in CARs to date can only bind a single target (such as CD19), limiting the range of cancers that can be targeted by the specific CAR (ie, only B cell malignances in the case of CD19 CAR-T cell therapy). Consequently, the breadth of targeting potential of the NKG2D binding domain makes this receptor attractive to generate a truly generic CAR-T cell therapy.

Celyad's first NKG2D CAR candidate is CYAD-01, an autologous CAR-T that started clinical testing in the company's first trial in 2017. CYAD-01 has generated early highly encouraging results in patients with relapsed/refractory AML with evidence of anti-leukemic activity and a 40% complete response rate. In the solid tumor arm of this study, there has been evidence of transient stable disease seen in patients with advanced colorectal cancer (CRC).

In these studies, no other treatment was co-administered, meaning the clinical effect could only be ascribed to the CAR-T cell effect. Celyad continues to optimize the therapy through working on scheduling the therapy dosing and combining with chemotherapy in order to determine whether a synergy can be found that optimizes the clinical response of the CYAD-01 therapy.

In parallel studies, Celyad has been pushing forward on allogeneic CAR-T cell therapy approaches. For many in the field, the molecular engineering used to eliminate the T-cell receptor is gene editing whereby the genome of the CAR-T cell is "edited" using technologies such as Talen, zinc fingers, or CRISPR-Cas9. These tech-

nologies cut the genome at the T-cell receptor alpha gene, which then repairs, effectively eliminating the T-cell receptor. In the second step of the process, a transduction using a vector carrying the CAR gene is then carried out, and the CAR-T cells are then expanded and banked ready for use.

Celyad has focused on non-gene editing approach. In the first version, a small peptide called the T-cell receptor Inhibitory Molecule (TIM) included into the CAR vector itself interferes with the ability of the T-cell receptor to deliver the signal to the T-cell that drives GvHD.[5] The TIM has been optimized to function with the NKG2D CAR to form CYAD-101, an allogeneic CAR-T cell product that is in clinical testing in patients with advanced colorectal cancer. Initial results of the first cohorts of this trial are expected in mid-2019.

In the second approach, Celyad has focused upon developing a non-gene edited platform suitable for any CAR. This approach uses short hairpin RNA (shRNA) to interfere with the expression of the T-cell receptor in the CAR-T cell. Data from recent preclinical studies have shown shRNA knockdown of TCR by targeting CD3 zeta is as effective as gene editing methods such as CRISPR/Cas9 (Figure 2). Once again, the shRNA is encoded within the CAR vector and with a single transduction step, allogeneic CAR-T cells can be generated, expanded, and banked ready for use. This shRNA approach is at an earlier stage of development and expected to enter clinical testing during 2020.

CELL MANUFACTURING

To ensure manufacturing does not slow down clinical development or commercialization of its therapies, very early on Celyad has established a top-tier manufacturing facility. Focusing on process development of their lead asset, Celyad has gained substantial cell yields compared to academic methods (Figure 3). The Mont-Saint-Guibert facility housing Good Manufacturing Practice (GMP), Quality Control (QC), and Quality Assurance (QA) departments offers more than 11 years of experience in personalized product manufacturing and is equipped to support over 1,000 patients annually, significantly increasing CAR-T supply capability. Additionally, Celyad's manufacturing plant can supply cryopreserved products to both US and EU clinical sites. By providing its CAR-T therapies to all clinical trials currently pursued, Celyad have positioned themselves to lead the way in production excellence of CAR-T therapies for the future.

SUMMARY

CAR-T therapies are recognized as breakthrough treatments in the landscape of hematological malignancies; the field now looks to investigate the potential of these therapies for solid tumors. CAR-Ts have been limited by several factors, including high production costs, medical complications in patients, and lack of therapies applicable to a broad range of cancer types. The development of immunotherapies employing natural killer cell receptors that recognize multiple NK-interacting ligands enhances the detection and destruction of tumor cells, vastly improving immune surveillance by CAR-T cells. Current advancements are driving the evolution of CAR-T therapies toward "off-the-shelf" - or allogeneic T-cells - modified to prevent or reduce the possibility of patients' developing GvHD, an immune challenge that is important to consider for any cellular transplant-like procedures. Most recently, Celyad's addition of shRNA into CAR-T cell technology aimed to knockdown TCR/immune response activation is another important step in this direction. By incorporating these new technological advances to their products, Celyad is engineering a platform for the next generation of CAR-T therapies with the hope of overcoming current limitations and bringing effective new treatment options for patients in need. ◆

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BIOGRAPHY

Dr. David Gilham is the Vice-President of R&D at Celyad, heading the implementation of Research and Development strategy programs in immuno-oncology. Dr. Gilham earned his PhD in Molecular Pharmacology at the University of Dundee prior to moving to Bristol University in 1996 to work on CAR-T cells with Professor Robert Hawkins. In 1998, he focused his research activity on engineering T-cells for cancer therapy and developing the necessary pre-clinical studies to support translation of this therapy into Phase 1/2 clinical trials in Manchester. He has also served as a Reader in the Institute of Cancer Sciences, University of Manchester, UK, and led the Clinical and Experimental Immunotherapy Group based within the Manchester Cancer Research Centre.

Drug Development
EXECUTIVE

Simon Edwards

President, CDMO Sales & Marketing

Cambrex

Cambrex: Providing Big Value in the Small Molecule Outsourcing Market

In today's market, most headlines tend to be focused on large molecules and can at times even hint that small molecules are dead. Although it may be true that much has changed since the first early chemical blockbusters, the popularity of small molecule drugs endures even to this day. As the global population continues to show little signs of slowing down, now more than ever we live in a medicine-focused society, and small molecules are at the cornerstone of it all. Existing in today's small molecule market requires flexibility and foresight as the trends shift and demand for outsourcing grows. Big Pharma is increasingly reducing its large investments into captive manufacturing facilities that age rapidly and are hard to maintain, whilst new small or virtual pharma companies lack the resources to dedicate to building or managing their own internal capabilities.

Cambrex, a contract manufacturing and development organization (CDMO) headquartered in the US with locations across North America and Europe, is committed to meeting these needs. The company provides pharmaceutical products, expertise, and technologies that accelerate small molecule therapeutics and has been in the business for nearly 40 years. Through recent strategic growth initiatives and the acquisitions of Halo Pharma and Avista Pharma Solutions, Cambrex now offers services and

"Not only did these investments significantly increase the customer base and funnel of projects, we are now able to partner with customers at any point or breadth across the whole lifecycle of small molecule drugs, from preclinical development through to commercial launch."

expertise from preclinical development, through to clinical Phase 1, Phase 2, and Phase 3 and into commercial-scale manufacturing for drug products.

Throughout the past 5 years, the executive team has been focused on making Cambrex THE small molecule provider of choice, and features locations in Europe (including Estonia, Sweden, UK, Germany, and Italy), Canada, and the US. Headquartered in NJ, with NC, IA, MA, and CO locations, the company employs more than 2,000 people and had 2018 net revenue of $532 million.

Drug Development & Delivery recently interviewed Simon Edwards, President, CDMO Sales & Marketing at Cambrex, to discuss the biggest trends in the small molecule outsourcing market.

Q: What has the past year looked like for Cambrex?

A: The past year has been active. Our team has focused in on a strategic transformation and expansion of capabilities across the full small molecule lifecycle to better serve customers. In 2018, we acquired Halo Pharma to expand formulation development and drug product GMP manufacturing, and in January 2019, we acquired Avista Pharma Solutions for early stage development and analytical services to support our existing drug substance and drug product expertise. These two acquisitions have allowed us to broaden and diversify our service offering in what is our continued mission to become THE leading small molecule company.

Not only did these investments significantly increase the customer base and funnel of projects, we are now able to partner with customers at any point or breadth across the whole lifecycle of small molecule drugs, from preclinical development through to commercial launch.

Q: What was the driver for the acquisitions, and how is integration going?

A: These investments were critical additions to our well-established active pharmaceutical ingredient (API) expertise to evolve with the industry and stay in step with customers who continue to seek more from their CDMO partner. The integration of Halo and Avista into Cambrex has allowed us to structure the business into three key offerings for our customers:

The drug substance offering incorporates the majority of the legacy Cambrex API business, including the development and manufacturing of innovator APIs; the scale-up and technical transfer of projects and analytical development; and specialist capabilities, such as handling of controlled and highly potent substances, continuous flow chemistry, biocatalysis, and solid state science.

The drug product offering features expertise in formulation and development of conventional dosage forms, including oral solids, liquids, creams, sterile and non-sterile ointments; as well as specialist capabilities, including developing and manufacturing highly complex and difficult-to-produce formulations, products for pediatric indications, and controlled substances.

Finally, with extensive analytical capabilities, such as solid-state chemistry, microbiology testing, cleanroom services, and material characterization added to our portfolio, we can support drug substance and drug product projects, or provide these as standalone services.

Following the integration of the two businesses into our global network, customer response has been extremely positive. We are now a truly world-class CDMO and will continue building on our platform of services and technologies.

Q: How has outsourcing (from a CDMO perspective) changed in the past 5 years?

A: As Big Pharma moves away from its reliance on a handful of blockbuster drugs to more specialized products serving smaller patient groups, they are faced with the prospect of trying to keep their large manufacturing facilities occupied or looking to divest or mothball old plants. We have seen these larger players outsourcing more of their projects in order to harness new manufacturing technologies that they currently do not have, as well as the small or virtual Pharma companies who lack any commercial manufacturing capability.

Q: What would you say to anyone suggesting that small molecules' days are numbered?

A: I believe these things just take time. I remember companies first heralding the arrival of monoclonal antibodies back in the 1980s. It has taken more than 30 years to get them to a point where they can be reliably manufactured and widely available to patients and even then some will argue they are only reserved for specialist care in the most serious diseases. I believe the same applies for other biological treatments, such as cell and gene therapies. There is no doubt they are emerging as life-saving medicines for previously untreatable diseases, but at the same time, there will always be a need for small molecules.

The market data clearly shows us that the small molecule pharmaceutical market is still big (pun intended) and continues to grow at the fastest rate seen in more than a decade. This is further fueled by a robust VC and PE funding environment for early stage companies and clinical programs leading to an increasing pipeline of new drugs.

From a commercial perspective, the FDA approved 42 small molecules in 2018, which is a 20-year high, and we continue to see more molecules moving between the clinical phases than ever before.

Q: What do you believe the future of small molecule outsourcing looks like? How can a provider remain competitive?

A: The size of the customer and their product portfolio will greatly impact what outsourcing looks like for them. We see that the smaller biotech and virtual pharma companies have little or no API development or commercial capabilities and will routinely outsource. For mid-size and big pharmaceutical companies, outsourcing small molecule API manufacture bridges internal gaps in capacity or capability, particularly when hazardous chemistry or specific technologies are required like with high-energy, high-potency, or controlled substance manufacturing. Based on industry and analyst projections, small molecule outsourcing is set to increase as more therapeutics are developed in smaller pharma companies at the same time as big pharma is increasing its spend in outsourced services.

To stay competitive, CDMOs need to offer flexibility in range of production (from kilograms to hundreds of metric tons) and have core technologies to accommodate the wide variety of customer projects.

From lab-scale to clinical-scale to commercial manufacturing, CDMOs must be able to adapt to the dynamic demands of the marketplace. Those willing to invest in technologies, such as continuous flow and high potency manufacturing facilities with a focus on quality, reliability, and flexibility, will see the greatest trajectory.

Q: How is Cambrex preparing for this future?

A: As a CDMO, success lies in the ability to serve the customer base and evolve with the industry. We must continually adapt and enhance our approach and resources to offer the most appropriate outsourcing solutions in terms of capacity, expertise, and technologies. This has been the principle behind Cambrex's investment strategy throughout the past 5 years. This approach enables our company to handle a wider variety of projects and chemistries while having the ability to be flexible in response to customer demands. ◆

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Dura Coat Combiseals - An Optimal Solution for Cartridge Applications

By: Carina Van Eester, MSCE

INTRODUCTION

In 2018, the average life expectancy of women worldwide was 74 years, and that of men 70 years.[1]The trend is continuing upward: by 2100, global life expectancy may reach 82.6 years.[2] In addition to improved living conditions, this rise in the average age of the world's population is made possible by better medical care with access to high-quality medicines and medical products. In order to keep the population as healthy as possible, it is not only necessary to ensure access to indispensable medicines, but also to continuously develop them further. Innovation, research, and improved use of medicines are key steps in ensuring that patients receive the safest and most effective medical care.

The global healthcare industry is facing major challenges to meet the stringent requirements and additional medical care needs associated with demographic change. Healthcare market players are striving to meet these expectations by investing in the continuous research and improvement of their products. With state-of-the-art medicines, it is essential that drug manufacturers can rely on appropriate sealing solutions that provide the best

FIGURE 1

Datwyler offers the most experience and knowledge in the cartridge applications industry.

possible protection for their products. Seals are one of the most important components for pharmaceutical drug packaging and have to meet high-quality requirements as they are in permanent contact with the drug product. In particular, elastomer and aluminum components used to seal the parenteral drug must be compatible with the drug it is housing, in addition to providing a flawless seal. It must be ensured that no contamination or chemical reactions occur between the drug and the elastomer component under any circumstances. Manufacturers of modern pharmaceutical and biotech drugs are thus confronted with major challenges.

CHALLENGES OF THE CARTRIDGE APPLICATIONS MARKET

Nowadays, pharmaceutical and biotech therapies for cartridge applications, such as dental care and insulin management, are becoming more prevalent – resulting in a constantly growing demand for high-end parenteral packaging solutions for these therapies. Because the market for cartridge applications has strict requirements, companies need a reliable partner to meet the challenges associated with meeting these requirements, specifically for parenteral packaging. As a leading supplier of sealing and packaging solutions of the highest quality and cleanliness, Datwyler offers its customers this assurance. The company's cartridge portfolio includes two core components: plungers and combiseals.

Datwyler's plungers can perform a wide variety of functions and have all of the physical, chemical, and functional properties essential to protect the integrity and efficacy of the drug. To ensure system integrity for the cartridges, in addition to high-quality plungers, advanced combiseal solutions are needed. It is important that combiseal components are multifunctional and offer multiple protections. Datwyler's components meet these requirements: even after multiple piercings, the combiseals maintain the integrity of the seal, while ensuring the lowest possible extractables and leachables profile for the application. A dual-compound elastomeric liner inside the aluminum cap provides optimal usability and a high resilience.

IMPROVED LAMINATION FOR THE NEXT GENERATION OF ALUMINUM SEALS

To guarantee the durability of the combiseals, they have to be extremely robust. Datwyler continues its efforts to improve its products and processes, and tackles this challenge with an advanced and industry-leading lamination for aluminum combiseals: Dura Coat. Datwyler's newly developed material combines a high-quality alloy with a protective laminate to create the ideal end product for cartridge applications.

The innovative technology uses state-of-the-art materials, which enables a clear reduction in particles during processing and handling. Furthermore, Dura Coat combiseals experience less abrasion than standard aluminum seals. Testing showed that the technology guarantees flawless processability in production and usage. Utilizing this proprietary technology helps to improve product robustness while also reducing the risk of drug product contamination.

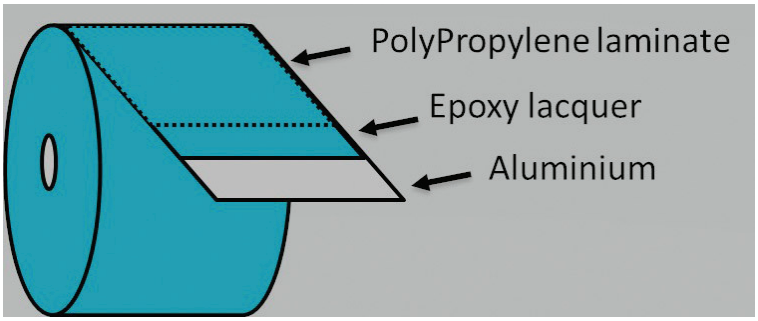
FIGURE 2

Datwyler's packaging solutions are compatible with all types of glass cartridges.

A Dura Coat laminated combiseal consists of an epoxy lacquer and polypropylene laminate that is applied to standard aluminum seals that meet the most stringent customer and authority requirements. The Dura Coat process begins with a high-quality, epoxy-based lacquer being applied to the aluminum. This step is followed by a protective polypropylene film being laminated on top of the lacquered layer.

When standard lacquered aluminum without protective laminate is manufactured, particles are naturally generated during various manufacturing processes, such as deep drawing, assembly, washing, and crimping. The Dura Coat technology reduces this particle generation up to 10x more than standard lacquered alloy. Cutting of standard aluminum after deep drawing – which is sometimes done to reduce earing – results in additional contam-

FIGURE 3



By combining these three layers, robustness is guaranteed.

ination of the combiseals with aluminum particles. As an additional quality measure, Datwyler is applying strict earing specifications to its aluminum suppliers in order to avoid cutting it after deep drawing.

COMPLETE PROTECTION REDUCES RISK OF CONTAMINATION

Unlike Dura Coat, standard epoxy-based lacquers are not very robust regarding flaking during production, transport, and filling. In addition, the transparent lacquer used on silver caps sheds particulates, but the flakes are barely visible and hard to detect during visual inspection. These flakes can eventually end up on the combiseal liner and, ultimately, contaminate the drug product. The Dura Coat protective laminate eliminates this issue. When the Dura Coat laminate is applied to a standard aluminum seal, the result is a durable and robust packaging solution.

The abrasion-resistant laminate also provides a protective barrier to external forces, reducing the risk of abrasion during manufacturing and handling. As a result, Dura Coat combiseals have less abrasion than standard aluminum seals. Abrasion can create visual defects, such as scratches, and can also produce flakes in the drug product which, particularly for high-end products and certain markets, are not acceptable. Datwyler offers a significantly low AQL (Acceptable Quality Limit) for this type of visual defect associated with combiseals laminated with Dura Coat.

In addition, Datwyler's Dura Coat combiseals are produced using best-in-class production technologies matching the quality expectations of the pharma market. All components are manufactured in a controlled environment operating under a zero-defect philosophy. Dura Coat not only meets the most stringent requirements for customers and authorities, but also provides the customers with the cleanest product available in the market.

DURA COAT: THE HIGHEST-QUALITY SOLUTION

A full suite of tests has been completed to ensure the effectiveness and functionality of the Dura Coat laminated aluminum. For example, a Taber test, which measures how resistant an object is to wear over time, was performed in accordance with ASTM D1044-08. The results of this testing show a significantly different wear resistance of the aluminum surface between non-coated (only epoxy-lacquered) and Dura Coat-treated aluminum. While the Taber equipment wears completely through the lacquer layer on the non-coated samples during 500 cycles, the color layer of the laminated material remains intact. This visual impression is also confirmed by the measured weight loss.

Depending on the customer's specific requirements and in order to provide unlimited functionality and flawless processability, a combiseal can undergo various steps before use. In order to make sure that the material withstands the different preconditioning processes, such as washing, sterilization, and drying before filling, a number of worst-case scenario tests have been conducted. This proof of quality ensures the material is as durable as the Dura Coat technology promises and that the customer receives a high-grade end product.

TAILOR-MADE FOR THE CUSTOMERS' NEEDS

When the plunger and combiseal components are integrated into the full delivery device, system functionality is imperative to ensure the treatment is delivered properly. With rigorous testing, Datwyler confirms that its plungers and combiseals are an effective packaging solution for cartridges.

As different applications require tailored and specific solutions, Datwyler faces this challenge with components that offer a variety of possible combinations of type (mono-layer or bi-layer) and compound:

- FM257: A Type I bromobutyl formulation that can be used for a broad application range of

buffered solutions. It is used as the contact side of the combiseal.

- FM457: A modern Type I bromobutyl formulation based on a unique polymer, which offers a very high chemical purity. It is used as the contact side of the combiseal.

- H1-7-207: A synthetic polyisoprene that is used for the non-contact side of the combiseal in order to improve sealing properties during multi-piercing.

Different liner compositions are available depending on the number of piercings anticipated. Mono-layer liners are used for single piercing applications, such as for dental care treatments. Bi-layer liners are used for multi-piercing applications, such as for biologics or insulin.

Depending on the intended use, Datwyler offers its customers suitable products and supports them in choosing the right components. The guidance in Figure 4 is offered to ensure the final functional properties of the cartridge.

These combinations have been tested according to ISO11040-3 (seals for dental local anesthetic cartridges) and ISO13926-3 (seals for pen-injectors for medical use) to ensure that sealing, as well as re-sealability and fragmentation, are guaranteed for the number of piercings for which it is recommended. Additionally, all combiseal components are available in silver, gold, red, green, and blue aluminum, based on customer preference.

FIGURE 4

Mono layer liner	Application	Thickness liner
FM257 or FM457	< 5 piercings	1,45 mm

Bi-layer liner (*contact compound)	Application	Thickness liner
FM257* or FM457* + H1-7-207	> 5 piercings < 50 piercings	1,45 mm
FM257* or FM457 + H1-7-207	> 50 piercings < 100 piercings	1,95 mm

Datwyler supplies its customers tailored combinations of components for cartridge applications.

TECHNOLOGY FOR THE FUTURE OF CARTRIDGE APPLICATIONS

The Dura Coat technology used for cartridge applications offers a very robust combiseal made of high-quality materials. Customers who choose Datwyler's solution benefit from a low particulate level and low visual defects due to a clear reduction of particles during processing and handling and less abrasion than standard aluminum seals. In addition, Dura Coat results in flawless processability and a seamless container closure. Dura Coat combiseals are the ideal solution for cartridge applications within the pharmaceutical and biotech markets. As access to safe and quality-assured medicines has a decisive influence on general healthcare and, therefore, on the expected average age of the worldwide population, progressive and reliable solutions are needed. A continuously improved drug therapy to increase efficacy fits perfectly with Datwyler's mission of "improving patients' lives." Datwyler combines years of experience and innovation to better serve its customers and help them create a safer medical environment.

With its innovative Dura Coat lamination technology, Datwyler is answering the demand for efficient, safe, and advanced delivery systems and drug packaging – and is taking healthcare a step further. ◆

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BIOGRAPHY

Carina Van Eester earned her Master's degree in Chemical Engineering and has been working in the pharma industry for 15 years as a packaging engineer. She has been working at Datwyler for 11 years. After many years of experience in Technical Key Account Management and Validation, she is now the Global Platform Leader for Prefilled Syringes and Cartridges, taking strategic initiatives related to Datwyler's components for these applications.

WEARABLE DEVICES

Wearable Drug Delivery Applications: Considerations for Adhesive Material Selection & Wear Testing

By: Neal Carty, PhD, MBA, and Deepak Prakash, MS, MBA

ABSTRACT

Wearable drug delivery applications can offer many patient care benefits, from easy administration to around-the-clock monitoring and medication management. However, if the device cannot comfortably and reliably be worn for the prescribed time period, it cannot deliver optimal outcomes. Also, as developers seek longer wear times to strengthen their devices' economic model, they need a clear understanding of how device design, construction, and adhesive material selection can be best aligned for extended wear solutions.

The following will discuss the broader healthcare and digital health landscape behind wearable device developments and provide a brief overview of two types of wearable applications — insulin pump therapy/continuous glucose monitoring (CGM) systems and wearable drug injectors. It will then focus on important considerations for adhesive material selection and wear testing of wearable drug delivery devices.

EVOLVING HEALTHCARE PARADIGMS

Behind the growth of wearable drug delivery applications are a powerful duo of drivers: lowering healthcare costs and increasing patient convenience. The healthcare industry is undergoing a transformation as players across its ecosystem strive to identify and adapt to less-expensive modes of care delivery.

"It is hard to dispute the notion that the mission of today's health systems, predominantly hospital-centric throughout the past 50+ years, is undergoing a significant transformation. Some might even refer to the transformation as happening at warp speed compared to the historically modest rates of change seen throughout the past few decades," said Brent McDonald, Head of Healthcare Strategic Advisory Services and Managing Director at Bank of America Merrill Lynch. Among factors impacting legacy healthcare systems, McDonald pointed to "the decrease in in-patient utilization due to technology and increase of other lower-cost and more convenient ambulatory/outpatient care settings."[1]

One of the most important lower-cost care settings is the patient's home. Telemedicine, whereby patients engage with their healthcare providers remotely, is on the rise. A Global Market Insight report valued the telemedicine market at $38.3 billion in 2018 and projected it will reach $130.5 billion by 2025. A Doximity study found telemedicine visits increased annually by 261% between 2015 and 2017. Factors prompting this growth include the physician shortage, more insurance reimbursement for telemedicine services, improved technology, and evidence of efficacy.[2]

Telemedicine is one component of a changing healthcare industry enabled by the Internet of Medical Things (IoMT). The Deloitte Centre for Health Solutions defined the IoMT as "a connected infrastructure of medical devices, software applications and health systems and services" in its 2018 report, "Medtech and the Internet of Medical Things: How connected devices are transforming healthcare." MarketsandMarkets valued the IoMT

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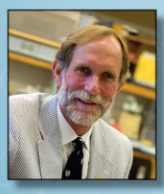

(Photo by: Will Kirk, Johns Hopkins University)

Peter Agre, M.D., co-recipient of the 2003 Nobel Prize in Chemistry, Bloomberg Distinguished Professor, and Director, Johns Hopkins Malaria Research Institute

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market at $41.2 billion in 2017 and expected it to rise to $158.1 billion in 2022, according to the Deloitte report. Of that total, the connected medical device segment is predicted to grow from $14.9 billion in 2017 to $52.2 billion in 2022. As an IoMT market application, medication management was valued at $6.6 billion in 2017.[3]

"The rise of the IoMT comes at a time when healthcare is becoming increasingly expensive, with global healthcare spending expected to grow 4.2% per year, from $7.1 trillion in 2015 to $8.7 trillion by 2020, largely due to a growing and ageing population, with more people living longer but with multiple comorbidities. As a result, without radical transformation, healthcare in many countries risks becoming increasingly unaffordable," said the Deloitte report.

Nestled amid the big picture of telemedicine and the IoMT is growth in self-administration of medications at home. When the patient's home is the drug delivery location, as opposed to a hospital or out-patient care facility, costs are lower. These savings are increasingly in the sights of pharmaceutical developers whose therapies already are quite expensive. There is a compelling impetus for them to develop drug formulations suited to self-injection instead of intravenous (IV) administration. "Recent years have seen groundbreaking advances in pharmaceutical development, with increasingly innovative medicines being brought to market every day. However, the cost and complexity of these novel drugs has intensified the pressure to shift medication administration from traditional settings to more cost-effective alternatives. One such alternative is the patient's own home, where life-altering molecules are now regularly self-administered subcutaneously to treat chronic diseases, such as rheumatoid arthritis, multiple sclerosis, and dyslipidemia among others,"" said Beth DiLauri, Director of Strategic Marketing, BD Medical, Pharmaceutical Systems, in a recent Drug Delivery & Development article, Wearable Injectors - BD Wearable Drug Delivery Devices: An Attractive Proposal.[4]

INSULIN DELIVERY SYSTEMS & WEARABLE INJECTORS OVERVIEW

Insulin Delivery Systems

Body-worn insulin delivery systems, including those with integrated CGM capabilities, are designed to help individuals with diabetes to manage this prevalent and costly chronic disease. An estimated 1.5 million people are diagnosed with diabetes in the US each year, according to the American Diabetes Association. The disease affects approximately 30.3 million Americans, or 9.4% of the population. Diabetes has a US economic cost of $327 billion, including $237 billion in direct medical costs and $90 billion in reduced productivity.[5]

Insulin delivery solutions come in many different shapes, sizes, and configurations. The most advanced are closed-loop systems, which act as a sort of artificial pancreas - continually monitoring the patient's glucose levels, administering insulin as needed, and alerting the patient of low- or high-glucose events. These systems have three primary components:

1. A body-worn sensor that measures glucose levels in the skin's interstitial fluid, usually by way of a tiny needle on the sensor's skin-facing side.
2. A transmitter, often integrated into the body-worn sensor, which sends the glucose data to a digital device, such as a smart phone or automated insulin dosing (AID) system receiver. These systems feature dosing algorithms that determine whether the patient needs insulin, and they may communicate directly with an insulin delivery device.
3. An insulin pump or pod that delivers the insulin into the patient's body, usually through a small cannula.

Dexcom, maker of the G6® Integrated Continuous Glucose Monitoring (iCGM) System, markets the technology, in part, by promoting how it provides an ongoing story versus a snapshot of the patient's glucose levels throughout the day and alleviates the need to do fingerpricks as frequently to check blood glucose levels. The Dexcom system integrates with Tandem Diabetes Care's t:slimX2™ insulin pump and Insulet's OmniPod Insulin Management System.[6] Medtronic, maker of the MiniMed™ 670G system with SmartGuard™ technology, said its system "automatically adapts to [the patient's] unique insulin needs every 5 minutes."[7] Abbott is the developer of the FreeStyle Libre CGS system, which it has plans to integrate with a new insulin pen from Novo Nordisk as well as Bigfoot Biomedical's insulin delivery solutions.[8,9]

Diabetes care may be only the beginning for wearable drug delivery systems with continuous monitoring. MobiHealth News reported in July 2019 that Abbott Executive Vice President of Finance and CFO Brian Yoor had this to say about other potential applications for FreeStyle Libre technology on a Q2 2019 earning calls: "I think [Libre has] got enormous potential,

FIGURE 1

Wearable devices often contain multiple layers of advanced medical materials. Whatever the combination, they must provide effective moisture management and biocompatibility for patient comfort. Image courtesy of Vancive Medical Technologies.

and it's got potential beyond glucose. It's got potential as a wearable and other analytes and other products over time. We have R&D programs underway not only for the repeated enhancements, improvements, expansion of Libre, but also into other categories beyond diabetes. I think there's a lot of things that'll evolve over the coming years that today people aren't even contemplating with the product."[10]

Wearable Injectors

Pharmaceutical companies and wearable medical device developers also are investing more R&D into formulations and device formats for wearable drug injectors, also known as on-body wearable injectors. The global market for wearable injectors is expected to grow from $5.57 billion in 2018 to $9.41 billion by 2023, according to MarketsandMarkets, which cites drivers including:

- increased prevalence of chronic diseases, such as cancer, diabetes, and cardiovascular disease
- more favorable reimbursement in major markets
- technology advances[11]

Wearable large-volume injectors (LVI) are a type of wearable injector that typically hold at least 2 mL of a drug. In a wearable injectors update published in ONdrugDelivery, Paul Jansen, Associate Vice President, Medical Device Development, Subcujet, predicted most LVI development will be in devices holding 3 mL to 10 mL. He said more than 3,000 injectable drugs are in development.[12]

In an overview for its December 2018 LVI research report, Roots Analysis said, "[LVI] are capable of drug delivery primarily via the subcutaneous route and have become a preferred choice for administration of drugs in the home-care setting."[13]

FACTORS AFFECTING WEAR TIME

Many wearable drug delivery device developers are seeking extended wear times. The economic case for a device often becomes stronger with longer wear times because there is not as much replacement cost. Extended wear times also can enhance patient convenience and compliance with a drug treatment plan. If a wearable device stays in position for extended periods, then there is less onus on the patient to remember to take his or her medication or to stop daily life activities to change out their drug delivery system sensor or injector. Whereas around 3 to 7 days previously was the wear-time norm, today, it is common for device developers to aim for 21- or 28-day wear times.

In recent years, there have been significant improvements in wearable device battery performance and other electronic and computing capabilities. Before these advances, a device's wear time often was dictated by battery life or data storage lim-

its. Now, adhesive material suppliers are focused on offering skin-friendly solutions that keep pace with extended wear times made possible by progress in other areas.

From an adhesive material perspective, a few of the most important factors affecting device wear time are moisture management, biocompatibility, and device design and construction. Each of these variables relate to one overarching goal: patient comfort.

Moisture Management

If moisture from perspiration or contact with fluids gathers on the skin beneath the wearable drug delivery system, the patient is likely to feel uncomfortable and could experience skin deterioration. This could lead the patient to remove the device prematurely or to experience an adverse event, such as a skin tear or infection. Most adhesive materials manage moisture in one of two ways. Either they absorb moisture and hold it away from the skin (fluid absorption), or they allow the moisture to pass through tiny pores in the material and evaporate (moisture vapor transmission). Some advanced medical materials leverage both moisture management methods.

Biocompatibility

If there are any irritants in the adhesive, the skin under the body-worn device can become itchy, red, or painful. Drug delivery system developers will want to be sure adhesive materials pass the ISO 10993 standard tests for cytotoxicity, irritation, and sensitivity, plus comply with local regulations by global region, and address allergen concerns relevant to the specific device end use.

Device Design & Construction

Adhesive material suppliers with wearable medical device experience can collaborate with drug delivery system developers on design and construction strategies to help ensure patient comfort as well as device manufacturability. For example, it is critical for the device construction to feature compatibility between skin-contact layer adhesives and construction-layer adhesives. The construction-layer material, also known as the tie-layer adhesive, is used to connect the skin contact layer to the device casing. Tie-layer materials often are double-sided adhesive tapes engineered to adhere properly to the skin-contact layer on one side and the device housing material (such as plastic) on the other. If the tie-layer tape's carrier material is non-porous, it can hinder or cancel the effectiveness of a porous (breathable) skin-contact layer material. In this case, it may be best for the device maker to use an absorbent skin-contact material. An experienced adhesive materials supplier can help recommend the appropriate mix of materials for the wearable drug delivery device application.

The adhesive release liner can also play an important role in manufacturability, device shelf-life, and the patient experience. An advanced adhesive materials supplier can advise device developers about which combination of adhesive and release chemistries will help their product to run most efficiently through roll-to-roll manufacturing lines. Release liners provide crucial support to delicate adhesive materials during production processes, such as rewinding, slitting, and die cutting. In addition, the materials supplier can recommend the best liner solution to properly protect the adhesive material through the device manufacturer's preferred sterilization method. Not all release chemistries are designed to withstand the same sterilization procedures. The liner also must remain securely in place, continuing to maintain the adhesive's integrity, through transportation and storage, and then be easy to remove by the patient.

WEAR TESTING OF DEVICE CONCEPTS

Even with the most thoughtful and collaborative approach to wearable device material selection and design, there is no substitute for wear testing a device concept to see how it feels and functions in actual use. Ideally, this testing, or "try storming," should take place during the early product conceptualization stage before the design freeze. Some materials suppliers will conduct this type of wear testing for customers to help identify optimal material choices and design elements — and to expose any unexpected problems with comfort and adherence.

A typical wear study, with appropriate statistical rigor, will involve a group of human volunteers that wear a device prototype (incorporating different material combinations) for the desired wear time, whether 7, 14, or 21 days or longer. Study participants can expose the device to different levels of activity, such as exercise and showering.

Sometimes the same group of people will then test a different device (one made with different materials or of a different design/construction) in order to offer a comparison of the wear experience. In other cases, the same device may be tested on some subjects worn on one part of the body (ie, abdomen) and tested on others worn on another area (ie, upper arm). Different body areas perspire at varied rates, and the amount of skin stretching and twist-

ing can also vary widely. Results can then be useful in unlocking the optimum design for the wearable product.

SUMMARY

As healthcare transforms to become more convenient, affordable, and effective for more people, connected medical device solutions will play an increasingly important role. Wearable drug delivery systems enable patients to more easily monitor their conditions and self-administer medications in the comfort and privacy of their homes. The most successful wearable devices will offer extended wear times and a high degree of comfort and discretion. To this end, adhesive material selection matters a great deal.

Wear testing during product conceptualization can help prove or disprove hypotheses regarding which material combinations, design elements, or application sites will be most comfortable and feasible for the end user. Sometimes this type of testing can expose issues that might be impossible to anticipate without a wear trial.◆

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BIOGRAPHIES

Dr. Neal Carty is Global Director, Research and Development, for Vancive Medical Technologies, an Avery Dennison business. He specializes in polymer science, having worked for Avery Dennison for 11 years. He earned his PhD in Chemical Engineering from the California Institute of Technology, his MBA from Case Western Reserve University, and his BS in Chemical Engineering from the University of Kentucky.

Deepak Prakash is Senior Director, Global Marketing, for Vancive Medical Technologies, an Avery Dennison business. He has over 20 years of healthcare experience spanning marketing and product development and has been employed with Avery Dennison for 9 years. He earned his master's degree in Chemical Engineering from the University of Akron, his MBA from Northwestern's Kellogg School of Management, and his Bachelor of Technology in Chemical Engineering from the National Institute of Technology Warangal.

DATA ANALYTICS

Leveraging Cloud-Based Data & Analytics to Optimize Pharmaceutical Manufacturing

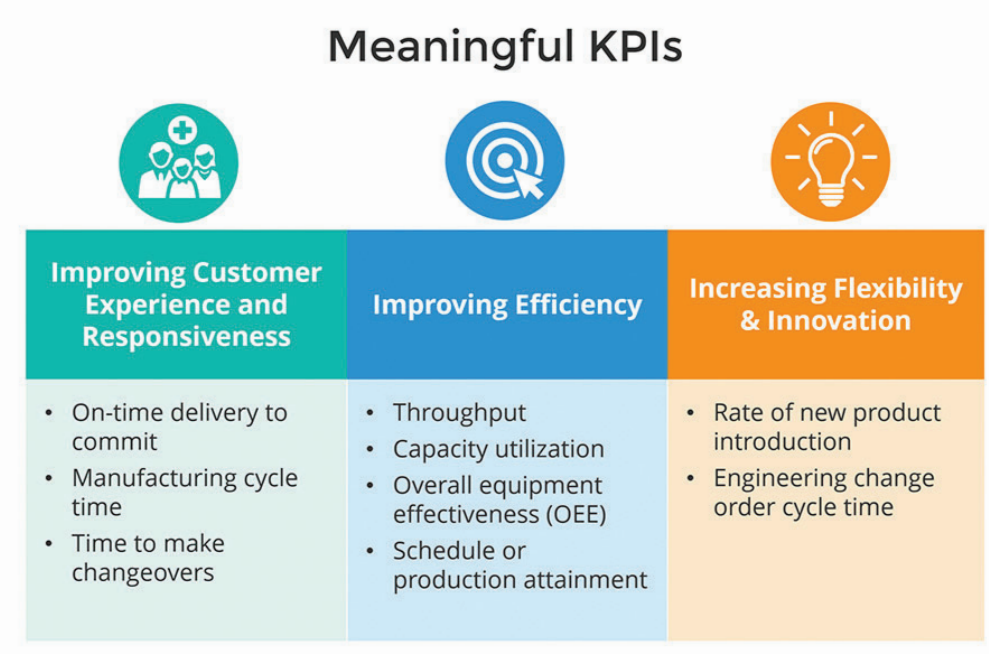
By: Benzi Mathew

INTRODUCTION

A pharmaceutical product's life cycle can be broken down, broadly, into three phases: clinical development, manufacturing, and commercialization. Increasingly, the life sciences industry is applying data analytics to clinical development to yield productive business insights that positively influence the drug development process. Analytic solutions are also being leveraged to optimize and inform marketing activities, including patient and HCP support and outreach. Bookended between clinical development and commercialization, manufacturing stands apart as an area that has remained largely untouched by the power of data analytics. That is starting to change.

Analytics in relation to operational efficiency has not traditionally been a focus area for biopharma. Life science companies are, by nature, innovators, so it makes sense that applications of data and analytics have, to date, primarily been applied to the discovery and development of therapeutics, as well as the creative marketing process. However, recognition is increasing about the powerful impact data and analytics can have on optimizing the manufacturing process and ensuring demand is met every time, all the time. A trend toward leveraging cloud-based technology to inform the visual factory has begun, and it is increasing manufacturing efficiency and productivity.

FIGURE 1



THE VISUAL FACTORY

The concept of the visual workplace, or factory, is a continuous process improvement paradigm that is an outgrowth of the Lean production process pioneered by Toyota in the late 1980s. A key concept of Lean process thinking is the elimination of Muda, the Japanese term for wastefulness or uselessness. A visual factory leverages visual representations of information, such as signs, charts, graphics, and other images, for quick dissemination of data within a Lean manufacturing process. The current status of all manufacturing procedures is thereby immediately apparent and accessible to all who need them. Time and resources needed to convey critical information are minimized, eliminating waste, but the availability and resulting impact of having that information readily available positively impacts the entire manufacturing flow. Streamlined communications yield maximum productivity, including:

- Reducing workflow problems, increasing product quality and productivity, as well as improving communication.
- Improving workplace safety by eliminating hazards and establishing compliance to work standards.
- Aligning employee efforts with goals and strategies for eliminating waste.

ANALYTICS & THE VISUAL FACTORY

Like most other industries, life science companies do their best to create efficient manufacturing operations, regularly reviewing, updating, and modernizing processes and procedures. However, according to McKinsey & Company, this is not enough:

"There's one significant asset that manufacturers have not yet optimized: their own data. Process industries generate enormous volumes of data, but many have failed to make use of this mountain of potential intelligence. Historically, manufacturers have lagged other industries in their IT capabilities. However, thanks to cheaper computational power and rapidly advancing analytics opportunities, process manufacturers can put that data to work, gathering information from multiple data sources and taking advantage of machine learning models and visualization platforms to uncover new ways to optimize their processes…"[1]

Data analytics can streamline manufacturing operations and provide ex-

FIGURE 2

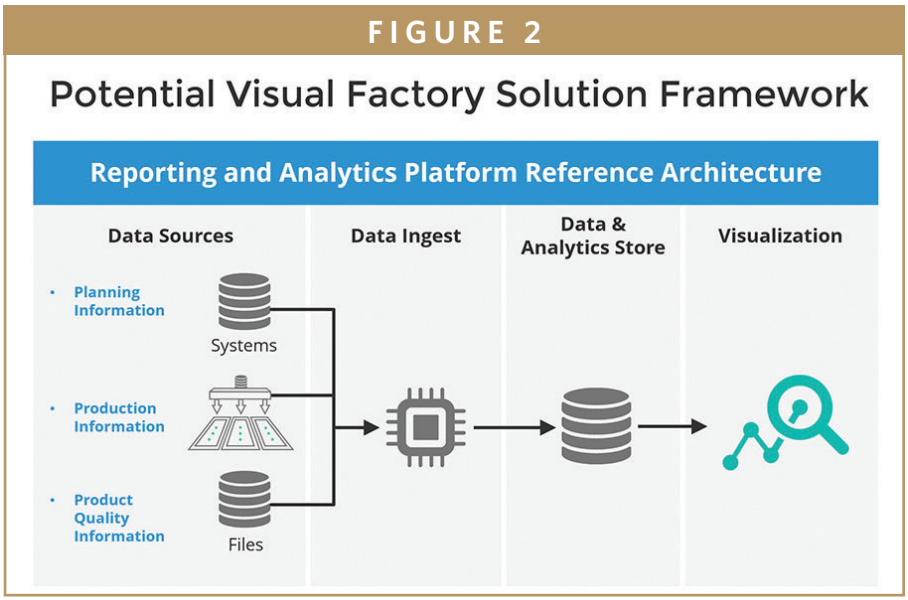
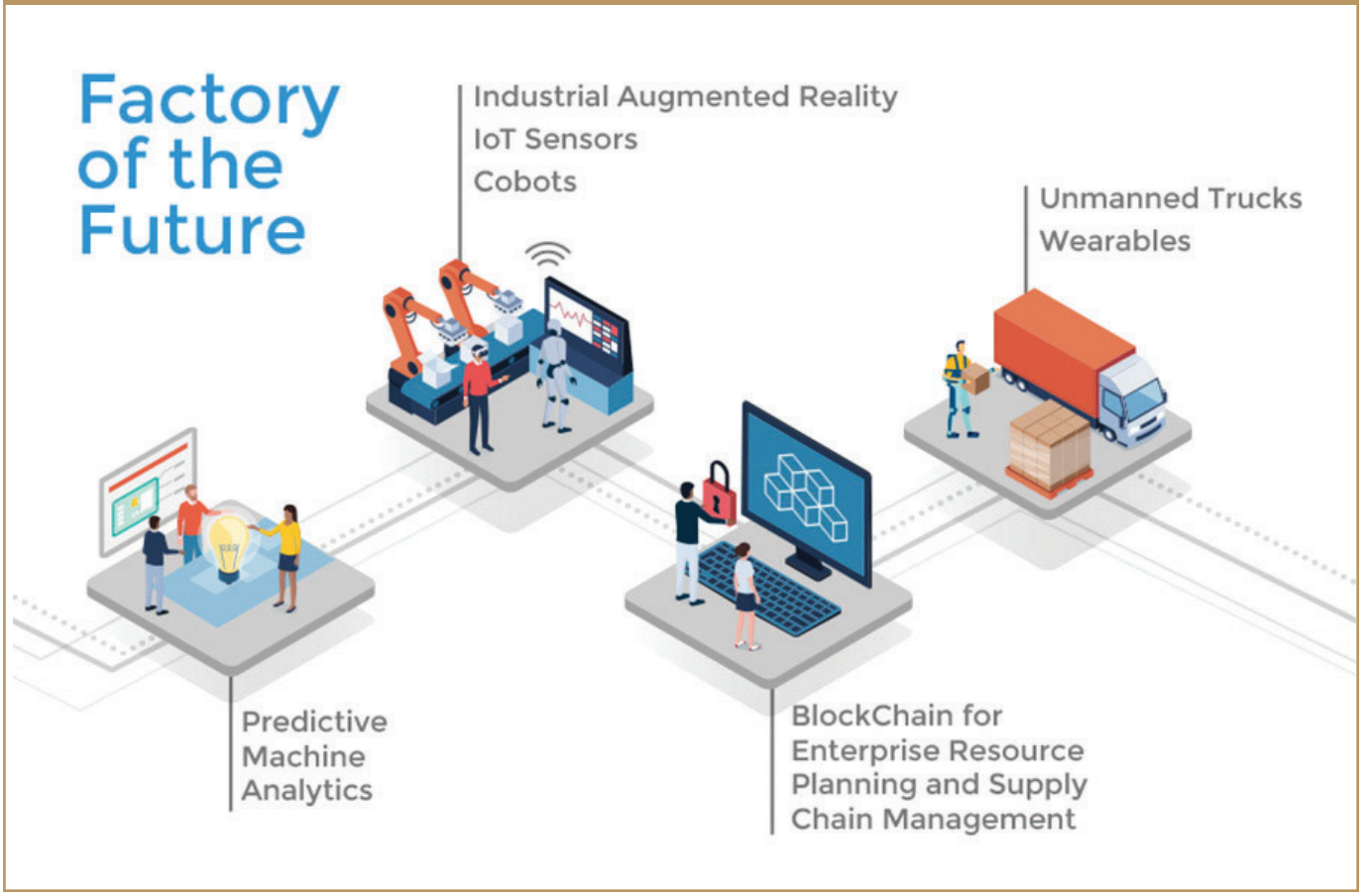


FIGURE 3

FIGURE 4



tremely focused and actionable insights that enable production line adjustments for inefficiencies related to issues as varied as machine down time, set-up time for lots, optimizing staffing mix, and shift changes. Results translate into minimized deviations to plans, in addition to time and cost savings. These outcomes are, to a large extent, technology agnostic. They are not reliant on one particular platform or solution, but rather can be addressed by any qualified cloud-based data and analytics technology that accelerates and connects disparate sources of data. Such real time and big data analytics essentially enable manufacturing systems to assess and identify their own correction needs.

In particular, there is a current trend for data and analytics to inform four main areas related to the concept of visual factories:

Measure & Monitor in Real Time: Cloud-based data and analytics technologies facilitate real time visibility to predict and propose immediate actions to ensure quality and make the manufacturing process more robust.

Solutions to Meet Unique Needs: Data and analytics not only help identify the unique, specified needs of individual factories, they support the formulation of tailored solutions. Facilities and lines manufacturing injectables clearly have different prerequisites and needs than those producing solid dose tablets. Preconfigured packaged functionalities covering usual, but hard-to-solve, industry requirements may not fit most facilities.

Qualified & Regulatory Compliance: Data and analytics platforms require continuous qualification to ensure the traceability of information and its data sources using regulated frameworks with specific solutions designed for this purpose. This process is imperative and must be respected.

Analysis & Knowledge Discovery: The approach used by a cloud-based data and analytics platform to find relationships between data, combined with the power of real time and big data analytics, enables customers to discover new optimization paths.

These trends ladder up to the objective that is at the heart of any application of cloud-based data and analytics to the

manufacturing process: simplifying factory operations. To achieve this goal, it is crucial to adhere to several guiding principles:

Start Simple: Keep the complexity low and demonstrate proof of concept and impact early on.

Focus on the Important Measures: Identify key performance indicators (KPIs) without being distracted by extraneous influences.

Identify the Change Drivers: These will guide process improvements.

Monitor Visually on the Factory Floor: Customizable, real-time alerts will enhance functionality, productivity, maintenance, collaboration, safety, and communication.

Prove it Works: Outcomes are key, so adhere to KPIs.

Remember That People Drive Changes: Analytics are designed to provide information that ultimately impacts human behavior. What use is valuable data unless it spurs someone to action?

Saama Analytics has developed the following summary of Meaningful KPIs for cloud-base analytics in the manufacturing process (Figure 1).

Saama recommends that each area of the manufacturing floor be governed by only the most relevant KPIs for that particular part of the manufacturing process. No more than 5 to 7 metrics should be made available visually per area, to ensure that the right analytics are reaching the right people at the right time. Saama deploys its Fluid Analytics Engine (FAE) to deliver scalable, cloud-based, advanced analytics solutions for manufacturers. Using a standards-based technology stack, FAE drives faster ROI and rapid time-to-market for modern analytics with flexibility and adaptability. As part of its core analytics engine, Saama's FAE includes data connectors and crawlers, security integrations, data models, data processors, advanced analytics integration, and visualizations. Such a potential visual factory solution framework is depicted in Figure 2.

Business needs drive all aspects of a biopharma operation, including user-centric visual analytics. Such analytics engage users, reduce risk, and accelerate time to value in the visual factory, as depicted in Figure 3.

SUMMARY

The data analytics-informed visual factory represents an exciting future for the manufacturing process. Simultaneously, it is also a stepping stone to the future; specifically the factory of the future – a manufacturing process in which every element of product production is guided by artificial intelligence and machine learning (Figure 4).

Until the factory of the future can be realized, however, the cloud-based visual factory can offer the life sciences industry as-of-yet untapped and unrealized competitive and economic advantages. By leveraging data analytics to fulfill product manufacturing demand every time, all of the time, biopharma companies will ensure that resources are efficiently deployed, inventories are optimized, and customer demand is met. ◆

REFERENCE

1. https://www.mckinsey.com/business-functions/operations/our-insights/manufacturing-analytics-unleashes-productivity-and-profitability

BIOGRAPHY

Benzi Alex Mathew is VP & Partner at Saama Analytics, and has been focused on the Life Sciences industry for almost two decades - trying to reinvent ways to help drive efficiencies through IT that helps Life Sciences companies reinvest savings into innovative new cures and improving access to affordable therapies for millions of patients. He and his teams are currently working with Pharma and Biopharma clients executing Analytics Innovation Lab experiments exploring the use of AI/ML, Data Science, Virtual Intelligent Assistants, Cloud Technologies, RPA, and Real World Analytics in the Commercial, Clinical, Manufacturing, HR, Finance, Legal, and IT functions. He is currently focused on setting up the Next-Generation Data & Analytics Operations model for Life Sciences companies to drive value 10x faster, better, and cheaper by integrating Data-Dev-Ops using modern technologies. Mr. Mathew is based out of Saama Analytics' Silicon Valley headquarters in Campbell, CA.

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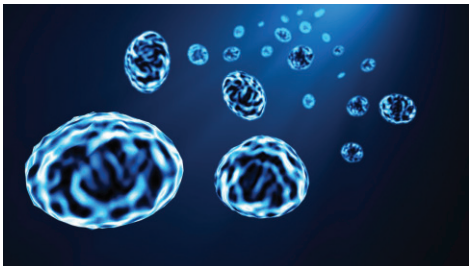

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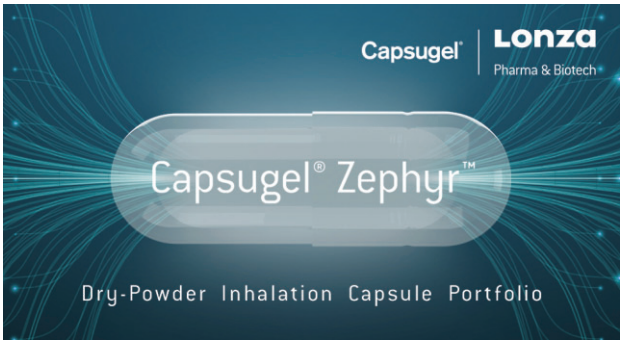

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