Drug Development & Delivery

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

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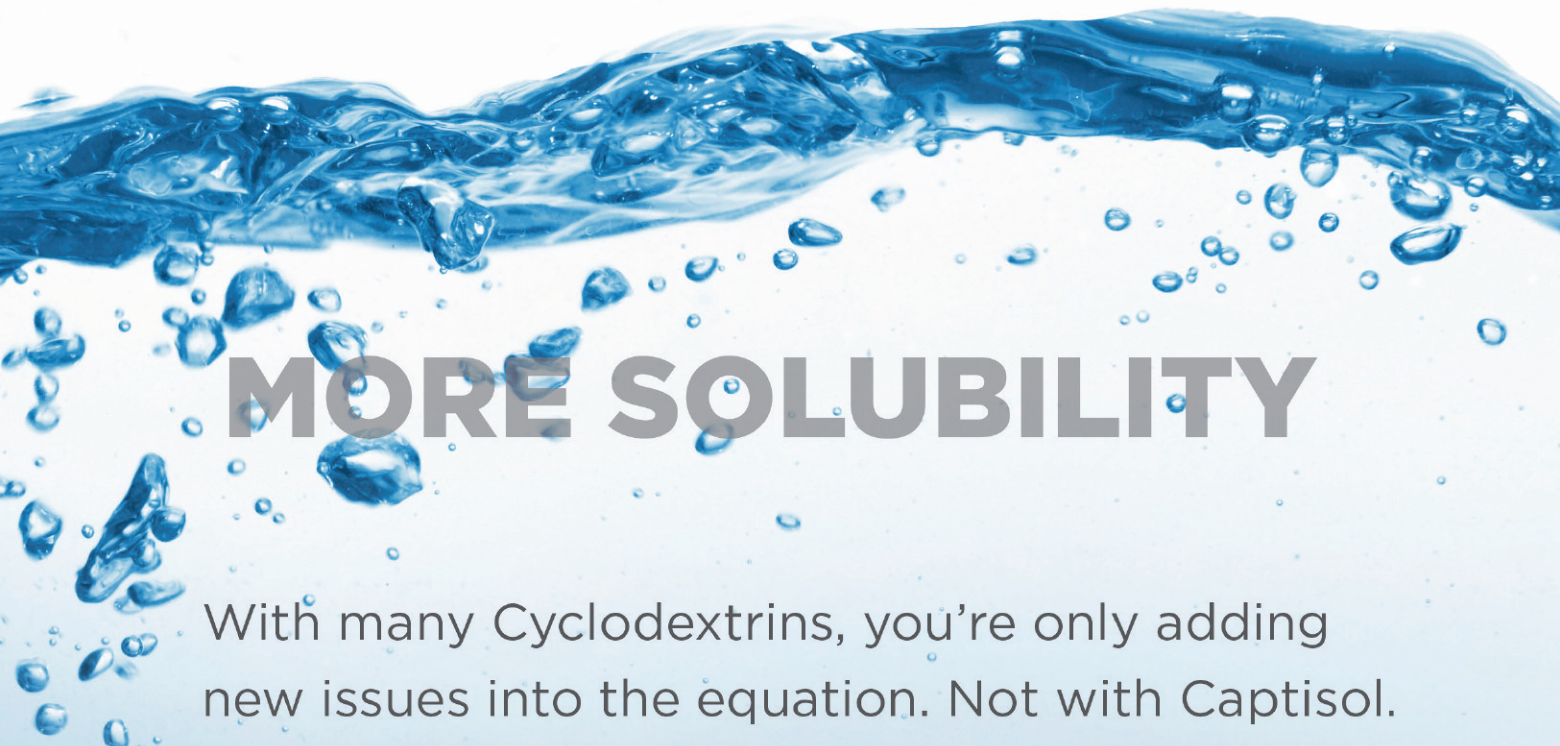

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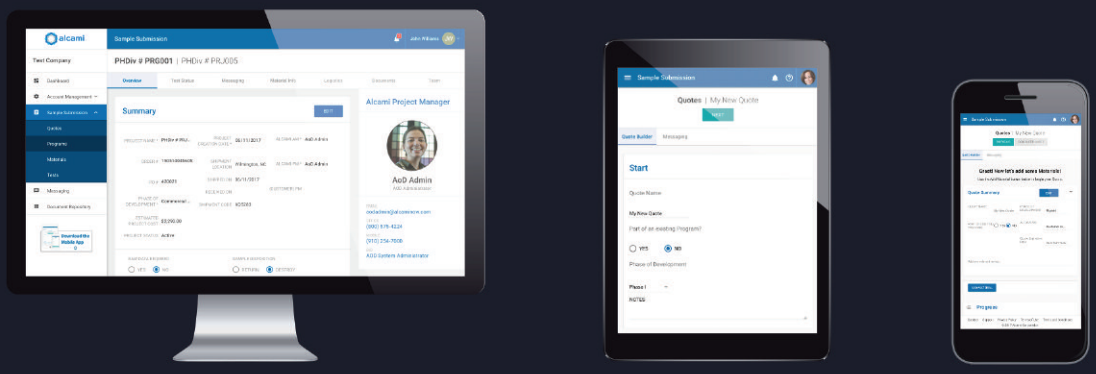

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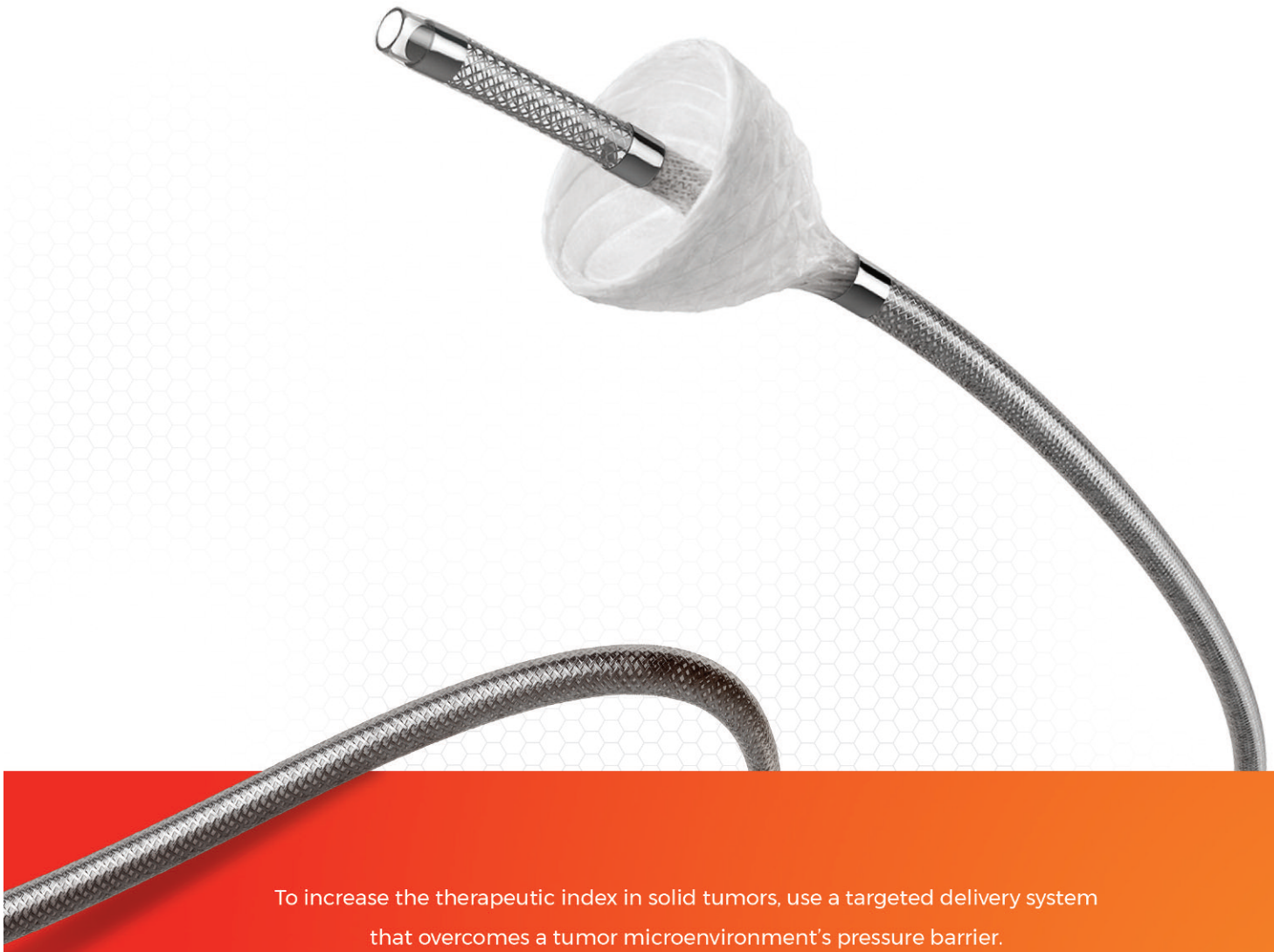
Want to increase therapy uptake in solid tumors?

Here's a tip.



To increase the therapeutic index in solid tumors, use a targeted delivery system that overcomes a tumor microenvironment's pressure barrier.

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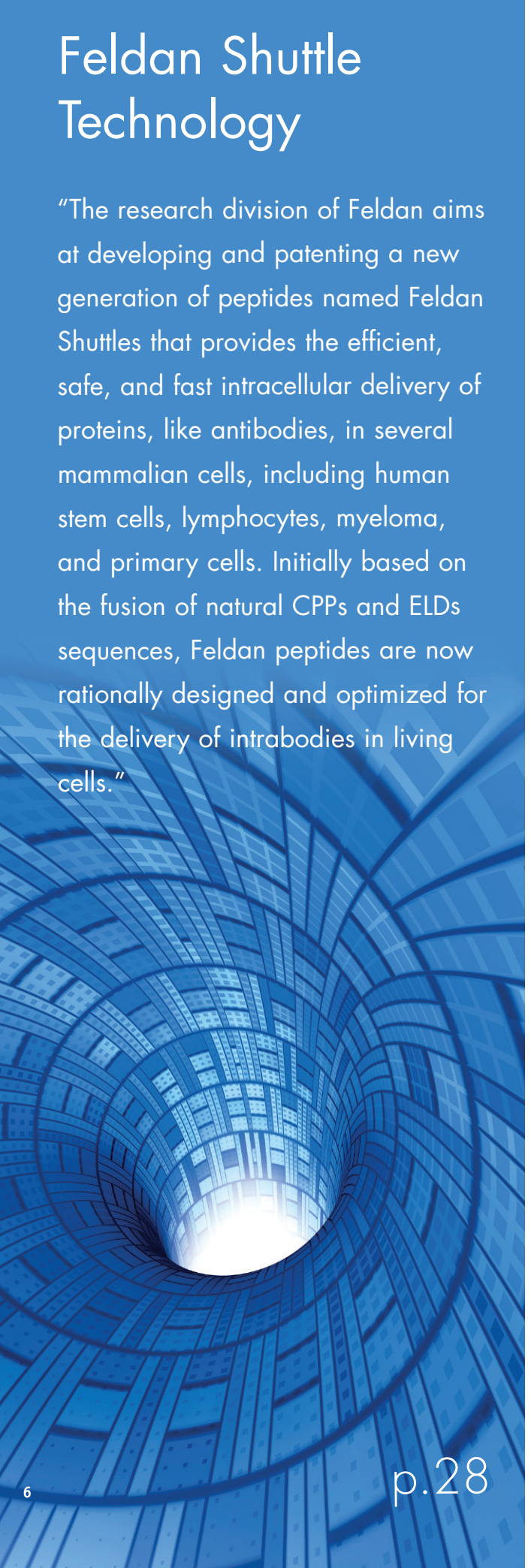
Feldan Shuttle Technology

"The research division of Feldan aims at developing and patenting a new generation of peptides named Feldan Shuttles that provides the efficient, safe, and fast intracellular delivery of proteins, like antibodies, in several mammalian cells, including human stem cells, lymphocytes, myeloma, and primary cells. Initially based on the fusion of natural CPPs and ELDs sequences, Feldan peptides are now rationally designed and optimized for the delivery of intrabodies in living cells."



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West Contract Manufacturing

Integrated Solutions for Cold Chain Pharmaceuticals

Helping to Make Cold Storage Less Complicated

Patient safety is of utmost concern in the pharmaceutical industry, with the FDA requiring drug manufacturers and their manufacturing partners to have strong quality management systems.

Temperature-sensitive drugs require storage solutions that not only meet the needs of the drug product, but also ensure compliance with regulatory guidelines in a properly monitored and sustained environment. Any deviation from the ideal environment can affect patient safety and jeopardize the drug's quality, resulting in loss of potency, efficacy or even the need to discard the product entirely.

Drug products such as biologics, vaccines, and products whose chemical and physio-chemical stability depends on temperature put an added emphasis on pharmaceutical manufacturers to ensure proper handling, storage, transportation and dispensing.

The West Contract Manufacturing team can support integrated device assembly solutions that meet regulatory and U.S. Food and Drug Administration guidance for temperature sensitive drug handling. This can help simplify the supply chain and reduce overall risk by improving production efficiencies.

West offers:

Clinical support

- Scalable solutions that support commercialization

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- Aggregation
- MES infrastructure
- Work cell history and analytics

As one of the largest custom manufacturers of reusable pens and auto injectors, the West Contract Manufacturing team can provide proper cold chain solutions – helping to ensure that temperature sensitive drugs are delivered to the patients who need them without compromising the integrity, efficacy, safety or security of the drug.

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Analytical Testing

"This has created a need to increase the production of drugs as well as develop new drugs to reduce the burden on existing ones. These factors are also increasing the demand for high-quality analytical services, for example, the desire for analytical and bioanalytical methods that address the growing market for complex compounds and biologics. Added to this complexity is the quickened pace at which service providers are expected to help progress these products into the clinic. To this end, contractors are enhancing their knowledge base."

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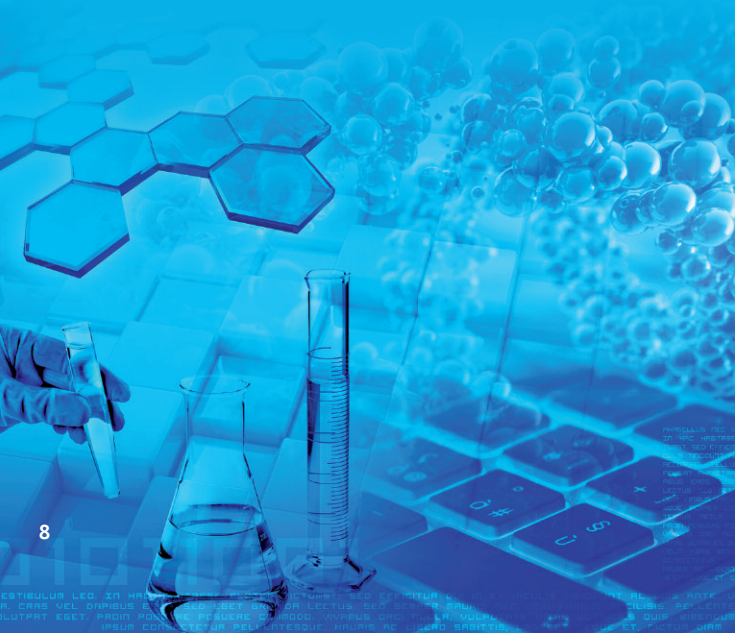

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Device training happens here.

There's life beyond chronic conditions. Distractions, anxiety and understanding correct administration technique can all affect compliance. Studies suggest 61% of patients don't completely read the IFU[1] and 12% of patients have proficient health literacy.[2]

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Reference: 1. Noble. (2015, November). The link between device training and patient compliance. Poster session presented at PDA - Universe of Prefilled Syringes 2015, Vienna, Austria. 2. Kessels, R. P. (2003, May). Patients' Memory for Medical Information. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC539473/

The Editorial Advisory Board

Carrick Therapeutics Announces First Patient Dosed in Phase I Clinical Trial

Carrick Therapeutics recently announced that the first patient has been dosed in the Phase 1 clinical program of CT7001 - an orally bioavailable Cyclin-dependent Kinase 7 (CDK7) selective inhibitor, that has shown striking efficacy in multiple preclinical cancer models.

We are excited by the potential of CT7001 to make a major difference in cancer treatment, and intend to rapidly progress CT7001 through clinical development and bring this promising new medicine to patients as quickly as possible. This is a significant achievement for Carrick to take a preclinical candidate to first patient dosed in less than 2 years," said Elaine Sullivan, Chief Executive of Carrick Therapeutics.

CDK7 inhibition has emerged as a promising strategy in a range of cancer indications. CDK7 acts as a master regulator of transcription, as well as a regulator of the cell cycle through phosphorylation of members of the CDK family. Inhibition of CDK7 suppresses the expression of key oncogenes such as c-Myc.

CT7001 was found to be effective in pre-clinical models of breast cancer, both hormone receptor positive and triple-negative, and transcriptionally driven cancers such as acute myeloid leukemia and small-cell lung cancer (SCLC). All these cancers continue to have major unmet medical need, for example, very little progress has been made for decades in the treatment of SCLC and triple-negative breast cancer (TNBC). Due to its differentiated mechanism, CT7001 is also predicted to be efficacious where resistance has developed to current therapies.

CT7001 originated from Cancer Research UK funded scientists at Imperial College London and was licensed to Carrick by the charity's Commercial Partnerships Team. Rapid subsequent preclinical development by the company's experienced research and development team has led to approval for the first-in-human phase I study. Efficacy studies are planned to start in 2018.

Carrick Therapeutics was established with an initial funding round that saw it raise $95 million, and continues to build its portfolio through partnering. Significantly, whilst other companies bank on a single molecule or biological mechanism, Carrick will build a portfolio that targets multiple mechanisms that drive cancer. In close partnership with a network of clinicians and scientists in internationally leading research institutes and hospitals, the business will drive its portfolio of ground-breaking cancer therapies from laboratories to the clinic.

The funding of Carrick Therapeutics was co-led by ARCH Venture Partners and Woodford Investment Management, with participation from Cambridge Enterprise, Cambridge Innovation Capital, Evotec, GV (formerly Google Ventures), and Lightstone Ventures.

Carrick Therapeutics is a biopharmaceutical company focusing on the innovative research and development of transformative oncology medicines. Carrick's aim is to become Europe's leading oncology biotech. The name Carrick means rock in Gaelic to emphasize the strong foundation of like-minded scientists, collaborators, and investors, and the vision to build a durable world-class company. Carrick has an ambitious patient focused vision to serve cancer patients around the world by the introduction of ground breaking cancer therapies that will transform the way cancer is treated.

LAM Therapeutics Announces Progress of its Clinical Portfolio With FDA Clearance

LAM Therapeutics, a 4Catalyzer company, advanced its clinical portfolio with the US FDA clearance of LAM's Investigational New Drug (IND) application for LAM-003 in leukemia patients. LAM-002 has transitioned into Phase 2 as a single agent and in combination with other therapies for treatment of B-cell non-Hodgkin lymphoma (B-NHL).

Identified by LAM's technology platform in 2016, LAM-003 is a first-in-class immune-modulating drug for treating a genetically-defined population of acute myeloid leukemia (AML) patients. "The short time from discovery to Phase 1 initiation highlights the power of LAM's strategy for leveraging high-throughput screening and patient-derived data to develop precision medicines faster and at a lower cost than conventional approaches," said Dr. Lieping Chen (co-discoverer of the PD-1/PD-L1 pathway, Co-Director Cancer Immunology Program, Yale Cancer Center, and Advisor to LAM). "We are excited about LAM's new therapeutic approach that is designed to overcome resistance observed with existing drugs used to treat AML, and we look forward to offering AML patients a new option for their disease," said Dr. Steven Gore (Director of Hematologic Malignancies, Yale University).

LAM further announced that clinical trial results for LAM-002, a first-in-class PIKfyve kinase inhibitor for B-cell malignancies, was presented on December 11, 2017, by Dr. Jeremy Abramson (Clinical Director, Center for Lymphoma, Massachusetts General Hospital) and Dr. Sarah Rutherford (Assistant Professor of Medicine, Weill Cornell Medical College) at the American Society of Hematology conference. LAM-002 was found to be safe and well-tolerated in the dose escalation portion of the trial, and anti-tumor activity was observed in patients who had failed multiple prior lines of therapy.

LAM has selected the recommended Phase 2 dose for LAM-002 and has initiated patient accrual; anti-tumor activity is being assessed in specific subtypes of B-NHL. "By taking advantage of artificial intelligence and Next Gen sequencing approaches, we are matching LAM-002 to patients who can most benefit from its novel mechanism of action," said Tian Xu (co-founder of LAM, CNH LONG Professor, Vice Chair of Genetics at Yale Medical School, Investigator at Howard Hughes Medical Institute).

LAM has partnered with Genentech, a member of the Roche group, who will provide the checkpoint inhibitor, atezolizumab (TECENTRIQ), to be used in combination with LAM-002 in B-NHL patients. "LAM is eager to collaborate with Genentech to test the novel mechanistic approach of treating patients with refractory lymphomas through the inhibition of both PIKfyve kinase and PD-L1. As published earlier this year in the journal Blood, we observed excellent synergy in animal models with both LAM-002 and anti-PD-L1, and LAM-002 with rituximab, and our Investigators are very enthusiastic about testing these innovative combinations in our trial," said Henri Lichenstein, President and CEO of LAM Therapeutics.

CytomX Therapeutics Announces FDA Acceptance of IND, Triggers Milestone

CytomX Therapeutics, Inc. recently announced that Bristol-Myers Squibb has received acceptance of the Investigational New Drug application (IND) from the US FDA for a CTLA-4-directed Probody therapeutic. CTLA-4, the clinically validated target of the Bristol-Myers Squibb checkpoint inhibitor Yervoy (ipilimumab), is the first target to advance into the clinic under the companies' strategic collaboration formed in May 2014. The IND acceptance results in a $10- million milestone payment to CytomX.

"Immune checkpoint inhibitors are making a profound impact in the treatment of people with cancer," said Sean McCarthy, President and Chief Executive Officer of CytomX Therapeutics. "By localizing antibody binding and therapeutic activity to the tumor microenvironment, our goal with Probody therapeutics is to deliver the same or potentially greater potency as first-generation checkpoint inhibitors, while reducing unwanted side effects. We are excited to see the CTLA-4 Probody advancing into the clinic and look forward to additional progress in our foundational alliance with Bristol-Myers Squibb."

In March 2017, Bristol-Myers Squibb and CytomX Therapeutics expanded their 2014 worldwide collaboration to discover, develop, and commercialize novel therapies using CytomX's proprietary Probody platform taking total upfront payments to CytomX to $275 million. The collaboration provides Bristol-Myers Squibb with the opportunity to select up to ten oncology targets and two non-oncology targets. To date, Bristol-Myers Squibb has selected five oncology targets under the collaboration, including CTLA-4. CytomX is eligible to receive additional preclinical payments and development, regulatory, and sales milestone payments totaling up to $4.7 billion across all 12 collaboration targets, as well as tiered royalties from mid-single digit to low-double digits on net sales of each product commercialized by Bristol-Myers Squibb.

CytomX Therapeutics is a clinical-stage biopharmaceutical company with a deep and differentiated oncology pipeline of investigational Probody therapeutics. Probody therapeutics are designed to exploit unique conditions of the tumor microenvironment to more effectively localize antibody binding and activity while limiting activity in healthy tissues. The Company's pipeline includes proprietary cancer immunotherapies against clinically validated targets, such as PD-L1, and first-in-class Probody drug conjugates against highly attractive targets, such as CD166 and CD71, which are considered to be inaccessible to conventional antibody drug conjugates due to their presence on healthy tissue. In addition to its wholly owned programs, CytomX has strategic collaborations with AbbVie, Bristol-Myers Squibb Company, Pfizer Inc., MD Anderson Cancer Center and ImmunoGen, Inc. For more information, visit www.cytomx.com or follow us on Twitter.

PhaseBio Enters Worldwide License Agreement With MedImmune

PhaseBio Pharmaceuticals, Inc. recently announced it has entered an exclusive, worldwide license agreement with MedImmune, the global biologics research and development arm of AstraZeneca, for PB2452 (formerly MEDI2452), a Phase 1-ready reversal agent for ticagrelor.

Ticagrelor is unique among P2Y12 antagonist antiplatelet agents due to its ability to reversibly bind to the receptor, whereas other P2Y12 antagonists bind permanently. Due to this unique mechanism of action, ticagrelor is the only oral antiplatelet with the potential to be reversed, should this be needed. PB2452 is an investigational, intravenous Fab antibody fragment designed to rapidly and specifically reverse the antiplatelet effects of ticagrelor in rare emergency situations. In preclinical studies, PB2452 demonstrated high affinity and specific binding to ticagrelor, and was shown to reverse ticagrelor-mediated inhibition of platelet aggregation and normalize bleeding.

"There is a clear need for treatments that reverse the effects of antiplatelet therapies in acute care situations, like urgent surgery or severe bleeding. PB2452's compelling preclinical data support its potential to be a first-in-class reversal agent for ticagrelor. The profile of PB2452 and the planned development pathway fits nicely with PhaseBio's niche focus on orphan cardiovascular disorders," said Jonathan P. Mow, Chief Executive Officer of PhaseBio. "We are excited that MedImmune has chosen to partner with PhaseBio for this medically important asset, which also allows us to diversify our pipeline beyond our ELP technology platform. We plan to initiate a Phase 1 study in the first half of 2018."

Cam Patterson, MD, a Cardiologist, Senior Vice President, and Chief Operating Officer of New York-Presbyterian/Weill Cornell Medical Center, added "PB2452 has the potential to reverse the antiplatelet effects of ticagrelor in rare emergency situations, while also reducing the current waiting period required ahead of emergency surgeries for patients on antiplatelet therapy."

PB2452 is a neutralizing Fab antibody fragment that binds to ticagrelor and its active metabolite AR-C124910XX, and is intended to reverse the antiplatelet effects of ticagrelor. The availability of PB2452 would enable reversal of the antiplatelet effects of ticagrelor in rare emergency situations and greatly reduce the waiting period before surgery.

Ticagrelor is a direct-acting P2Y12 receptor antagonist in a chemical class called cyclo-pentyl-triazolo-pyrimidines. Ticagrelor works by inhibiting platelet activation and has been shown to reduce the rate of atherothrombotic cardiovascular (CV) events, such as heart attack or CV death, in patients with acute coronary syndromes (ACS). Ticagrelor, co-administered with aspirin, also known as acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with ACS, or for patients with a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.

PhaseBio Pharmaceuticals, Inc., is a clinical-stage biopharmaceutical company developing therapies for the treatment of orphan diseases. PhaseBio is leveraging its proprietary elastin-like polypeptide (ELP) biopolymer technology platform to develop therapies with the potential for less-frequent dosing and better patient compliance.

PARTICLE DESIGN TECHNOLOGIES

Technical Guide for Solid Dispersion Development

By: Nathan Barksdale and Elizabeth Hickman, MBA

INTRODUCTION

The number of pipeline drug candidates that are poorly soluble, falling into Developability Classification System (DCS) Class IIa, IIb, and IV, continues to increase. The poorly soluble nature of these compounds leads to poor absorption, poor bioavailability, and increased pharmacokinetic variability. Clinically, these features result in drugs with poor efficacy and safety profiles. Because many of these drugs exist as crystalline materials, the answer may lie in creating an amorphous solid dispersion (ASD) for which spray drying technology is a key part of the manufacturing process. There are many articles on the theory and scientific principles underpinning the benefits of ASD. This article aims to introduce the reader to the steps involved in the development and manufacturing of an ASD via the spray drying process.

HOW DOES SPRAY DRYING WORK?

An ASD comprises a mixture of the API in its amorphous state, with at least one polymeric carrier excipient that has a single glass transition temperature, and no detectable crystalline structure. These mixtures are created by dissolving the API and the polymer excipient (or excipients) in at least one strong, volatile solvent, and then rapidly removing those solvents. The spray and evaporation rates are crucial: the evaporation must take place before either crystallization or phase separation has time to occur.

The high speed of the spray drying process makes it an essential tool in the creation of amorphous forms. The API is in solution, and the spray dryer very rapidly evaporates the solvent into a vapor, leaving behind the API as a dry solid. To achieve this, the solution is sprayed into a drying chamber through a narrow nozzle that creates very fine droplets, and solids form as the solvent evaporates. Spray drying of only the API is not sufficient as the particle will have a high tendency to rapidly re-crystallize. Therefore, a hydrophilic polymer is added to inhibit or retard re-crystallization, as well as improve the solubility and dissolution rate of the API (Figure 1).

Particle size, density, compressibility, and residual solvent levels are some of the main parameters to assess the quality of the spray-dried particles and their robustness to be further incorporated into a final dosage form. The resulting particle size that is formed is important both in terms of performance and powder handling, and is determined by the spray pattern of the droplets of solution that emerge from the nozzle, as well as the tension and viscosity of the solution, the solids content, the spray rate, and the atomization gas that is used. Density and compressibility (important parameters in the ability of the powder to be formulated into a tablet) are related to particle size and the inlet and outlet temperature. The optimization of the inlet and outlet temperature range is critical for controlling the drying kinetics, which impact the final particle morphology. Any residual solvent will have an impact on physical stability.

BENEFITS OF CREATING ASDS

An amorphous dosage form is typically not the first choice for a drug formulator, as other approaches such as salt forms, co-crystals, and micronization, are likely to be less costly and require a lower degree of technical expertise to manufacture at larger scale. If none of these approaches give the desired solubility, then

it is worthwhile to assess the development of an amorphous dosage form.

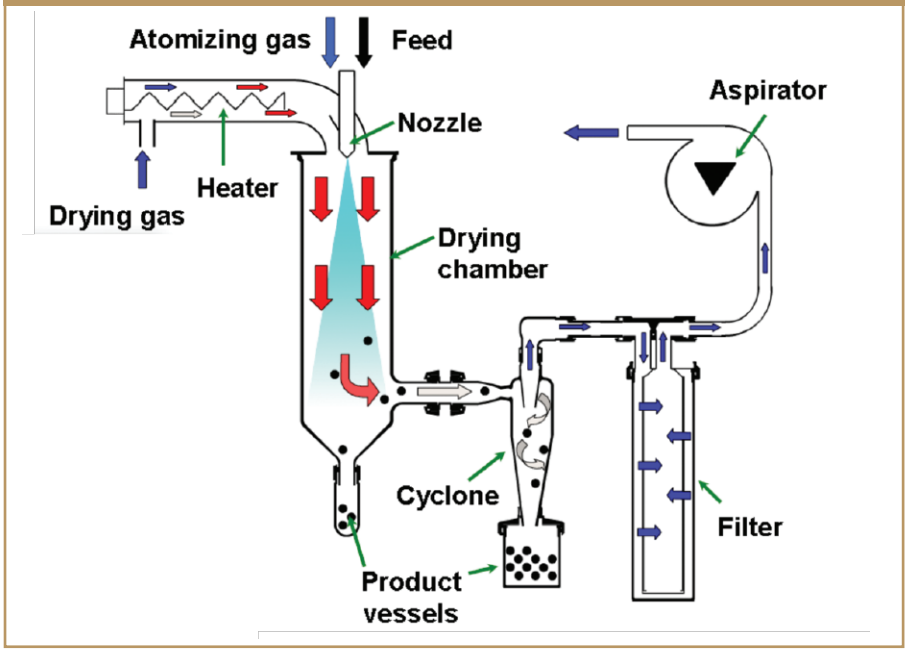
Cases in which this has proved to be the best option include APIs in which polymorphic form (different crystalline structures) control has been problematic, as the amorphous form gives process control over polymorphs. It can also assist where residual solvents or particle size distribution have been difficult to control during API synthesis.

The method also offers an alternative method when looking to increase the solubility in the gastric and intestinal fluids of APIs that fall into Class II of the Biopharmaceutical Classification System (BCS), or Class IIb (solubility-limited absorption) of the DCS. Amorphous forms are intrinsically more soluble, as there is no crystalline lattice energy to be overcome. It is advantageous to have a resultant finely divided powder that can be processed into any dosage form that can incorporate powders, including capsules and tablets.

Conversely, there are some APIs that are never likely to be appropriate candidates for an amorphous dosage form because of the high energy of the powders. These include APIs that are inherently unstable, where chemical degradation is possible, or where the API is particularly hygroscopic.

Manufacturing considerations can also remove the amorphous form as an option. Complex enhancement steps are required in the process, such as spray drying, hot melt extrusion (HME) or Wurster coating, and secondary processing, such as tray drying, granulation, or compression, increases the complexity of manufacturing. It should also be noted that there are usually more in-process, release, and stability testing requirements to be met for an amorphous dose than alternative methods.

FIGURE 1



PREFORMULATION SCREENING

The first step in creating the formulation is to screen a range of parameters that describe the API's physicochemical characteristics and determine the composition of the formulation. These include the form in which the drug will be incorporated into the dose, such as a salt or the free form, and determining whether there are any known polymorphic forms or solvates whose formation will need to be monitored. The API's baseline solubility at 37°C in different biologically relevant media [fasted-state simulated gastric fluid (FaSSGF), fasted-state simulated intestinal fluid (FaSSIF) and fed-state simulated intestinal fluid (FeSSIF)] should be established, along with its DCS categorization and the solubility limited absorbable dose (SLAD).

Additionally, the API's solubility and stability in common volatile solvents (water, ethanol, methanol, isopropanol, hexane, acetone, dichloromethane, tetrahydrofuran, and ethyl acetate) should be assessed. The solubility of the most stable polymorphic form of the free-form API should be measured, and the stability study should be monitored at both ambient and accelerated temperatures for 3 to 7 days.

It is not uncommon that the API will not have sufficient solubility in a single solvent, so a combination of solvents can be used. In solvent combination screening, two to four solvents are selected that give the best solubility and stability results in the initial screen, and tests should be undertaken to further measure the solubility and stability of the API in 20:80 and 80:20 mixtures of all possible pairs of the solvents. The combinations that give the most acceptable solubility and chemical stability characteristics should then be used for those spray drying tests, but it is preferable that one predominate solvent is used whenever possible.

If multiple solvent systems with solubility greater than 50 mg/g and stability for 3 days at accelerated temperature are identified, then it is safe to move on to initial spray drying tests. If not, then solubility and stability need to be optimized, which can usually be achieved through solvent combination screening.

POLYMER SCREENING

Amorphous APIs by definition are in a high-energy, unstable state. The driving force for the API is to revert into its low-energy, stable crystalline state. Excipients, specifically polymers, are used to inhibit or delay crystallization, which in turn affects the physical stability, dissolution rate, supersaturation level, and bioavailability of the API.

Identifying the best polymer excipient, or a combination of them, is an important step in creating the optimal spray dried powder. Ideally, between two and six such polymers will be selected for screening; the four most common are hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), polyvinylpyrrolidone/vinyl acetate (PVP-VA), and hydroxypropyl methylcellulose acetate succinate (HPMC-AS). Batches of between 1 and 5 g should be prepared with a 15% to 25% API loading in each polymer system – the same percentage loading should be used for each different polymer.

Once the test batches have been spray dried, the homogeneity of the amorphous product is assessed by differential scanning calorimetry (DSC). It is also important to assess the amorphous system's potential to reach supersaturation levels in relevant biological media, such as simulated gastric fluid (SGF), FaSSIF, and FeSSIF.

After establishing the initial screening results, the next step is to focus on the optimal polymer choice and the best loading rate. Between one and three polymers that have appeared promising in the rapid screen are chosen, and batches of several loads ranging from 10% to 75% of active, based on pre-formulation data are produced. The polymers are sprayed at selective loads on a 1 to 5 g scale, and then kinetic solubility testing versus load is performed.

Physical and chemical stability of these samples is assessed in several ways. Samples at the various loading levels should be stressed to induce crystallization, if possible, and to allow for any chemical incompatibilities to be detected. In addition to DSC studies, powder X-ray diffraction (PXRD) experiments are performed to assess crystallinity, and high-performance liquid chromatography (HPLC) is used to assess chemical stability. Both water content and visual appearance are also assessed.

With these data in hand, the next step is to select a lead dispersion. Chemically incompatible polymers or loads can be pinpointed by comparing sealed and open dishes that have been left open to the atmosphere for a period of time, and if any degradation is observed, whether this is a result of the polymer or the exposure to moisture in the atmosphere. It may be possible to improve stability with appropriate packaging or moisture protection measures, and if this is the case, poor results at this stage will not necessarily result in failure of the dispersion.

Similarly, those polymers and loads that are physically incompatible should be identified. Phase separation or crystallization will be problematic if they occur in the finished dosage form, but again, it may be possible to avoid these with suitable packaging.

Those batches that do not fail for stability reasons can then be assessed for overall suitability and the selected samples screened individually, using a bio-relevant kinetic solubility test to identify which have the highest levels of solubility. The DCS is then revisited, to assess whether the spray-dried samples are likely to have improved properties if an amorphous dosage form is created. Ideally, the solubility of the final spray-dried system will be high enough to increase the DCS IIb rank to either DCS IIa or DCS I rank.

LABORATORY-SCALE SPRAY DRYING TESTS

The first step of spray dry process development is the running of feasibility batches, which can be prepared on a gram scale and are designed to identify the optimal solvent systems, polymer excipients, solids content and active loading level, as well as verifying the amorphous content and stability of the spray-dried powder.

There are broadly two designs of spray dryer that can be employed: the open loop system and the closed loop system. Both have their advantages and drawbacks; with an open loop system, the solvent saturation will be low; however, there is a much higher explosion risk because of the inevitable combination of oxygen, heat, and fuel. In contrast, the closed loop system does not pose this risk of explosion as the system is flooded with nitrogen rather than being open to the air. As well as being safer, it is also faster, more scalable, and the design is more environmentally friendly. On the down side, the solvent saturation is much higher.

Several small-scale spray dryers are available from commercial sources, and again, all have their advantages and disadvantages so, ultimately, the choice comes down to the nature of the material that is being spray dried. The ideal small-scale spray dryer will offer the ability to carry out particle engineering experiments

that are representative of what will happen on a larger scale, and the ability to tailor particles for inhalation applications. It should give a high yield for platforms screening batches, be easy to customize, and offer continuous spraying.

SPRAY DRYING SCALE-UP

To move from the laboratory scale to commercial manufacture, the spray drying process must clearly be carried out on a much larger scale. The solvent system, polymer, and drug loading will have already been determined, and larger batches will need to be made for preclinical animal studies, GLP studies, and eventually GMP manufacturing to support clinical trials and commercial launch.

The sort of lab-scale spray drying equipment used for those small test batches is wholly insufficient in capacity to support larger scale work, as the maximum batch size is around one kilogram.

Spray dryers, such as a GEA Niro Mobile Minor™ machine, are used for the next step of development at pilot scale. This equipment permits continuous operation in a closed cycle system and has a maximum evaporative capacity of about 2 kg of water per hour, and the option of 10- to 350-L jacketed mixing systems.

There are two options for nozzle selection: a two-fluid nozzle or a high pressure nozzle. The former requires a peristaltic pump and atomization gas, and 0.5–1.5 mm tips are available. Particle-size control can be achieved by altering the ratio of atomization gas to liquid flow rate: increasing the liquid flow rate will give larger particles; increasing the gas flow rate will give smaller particles.

With a high pressure nozzle, there is not atomization gas; rather, it employs a pressurized diaphragm pump. Tips range from 0.1 to 0.4 mm, and the spray angle can be varied from 45° to 120°. Increasing the flow rate increases the pressure, which gives a tighter distribution of smaller particles. In contrast to the two-fluid nozzle, which is only really appropriate at lab scale, the high-pressure nozzle can be used to make much larger quantities. In addition, where the two-fluid nozzle has very high consumption of nitrogen, none is needed for the high pressure nozzle.

When planning a scale-up, several parameters need to be considered in addition to the nozzle and tip size. These include pressure and liquid flow rate, the nature of the drying gas and its flow rate and temperature, and the outlet temperature in the control of residual solvent and saturation.

To remove residual solvent and reduce its impact on the stability of the final API, when spray drying on large-scale equipment, a secondary drying process is necessary, which will typically be carried out in a vacuum oven or granulation dryer depending on the scale. It is important that the spray-dried substance meets International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for residual solvent Q3C(R6) and USP <467> residual solvents.

Drying studies should be run to check whether the solvent removal is adequate. This can be done by storing the material in a drying oven, sampling at multiple time points, and sampling for residual solvent via gas chromatography.

Roller compaction is typically performed as a final step to increase the particle size and density, and in this process, the powder is forced through two counter-rotating rollers to increase the density and compact the powder into ribbons. These ribbons are then milled to give uniform granules. The powder that emerges from the roller compactor has greatly improved flow properties, with a typical bulk density of 0.5 to 0.7 g per cubic centimeter. This is important when compressing tablets or manufacturing capsules, as it will give better weight and content uniformity to the final dose form.

DOSAGE FORM SELECTION

With a dispersion in hand that is both physically and chemically stable, as well as providing adequate solubility enhancement, the next step is to look at using it to create the most appropriate solid dosage form, whether this is a tablet, a capsule, or some alternative format. It is important that potential excipients required to make the dosage form should be selected and tested for compatibility with the spray-dried powder; however, the manufacturability and disintegration must also be considered when selecting excipients and developing a formulation.

When assessing the compatibility of excipients, both binary mixtures and design of experiment (DoE) studies are suitable. Previous stability data gathered with the crystalline drug should be reconsidered, and all samples should be made using the lead amorphous dispersion material. The use of the final amorphous intermediate is crucial for excipient compatibility studies, as amorphous forms are more sensitive to degradation, but it is also important to consider moisture protection in the study.

Formulation development efforts should be focused on creating dosage

forms with fast disintegration times, with dissolution being monitored for gelling. It may be appropriate to consider more aggressive disintegration approaches if initial attempts produce long disintegration times, or slow dissolution rates. These might include the incorporation of high levels of bicarbonate, an osmogen (high-water solubility excipients), or a super-disintegrant. All *in vitro* formulation development work should be confirmed with *in vivo* studies whenever possible and the neat dispersion suspended in water along with the formulated dispersion product should be compared in a relevant model to ensure poor disintegration is not leading to lower than expected exposure levels. If the final dosage form is not formulated so that rapid, consistent disintegration is achieved, then the increased solubility can be quickly negated by the poor release of the spray dried intermediate. Formulation processes to increase density and reduce surface area can slow down the spray-dried intermediate's wetting rate, allowing the final dosage form to disintegrate fully without forming a gel.

The quick identification of a suitable dispersion is not a trivial exercise, not least because disintegration, flow, and density challenges are amplified when developing a spray dried amorphous product. Although pursuing ASD formulation may extend timelines and introduce complexities not seen with traditional tablets and powder-filled capsules, implementation of DoE and working with an experienced partner can help avoid bottlenecks and program delays. Time and cost savings can be realized by formulating DCS IIb drugs to address bioavailability challenges prior to first-in-human studies and avoid the need to go back and re-formulate. A study at GlaxoSmithKline showed that for DCS IIb compounds, it takes 2 additional years of performing clinical studies to reach a decision to stop development because a compound does not have adequate exposure to reach sufficient efficacy.[1] Spray drying and amorphous formulations can be very powerful tools to increase solubility and bioavailability within a traditional dosage forms such as a capsule or tablet. ◆

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BIOGRAPHIES

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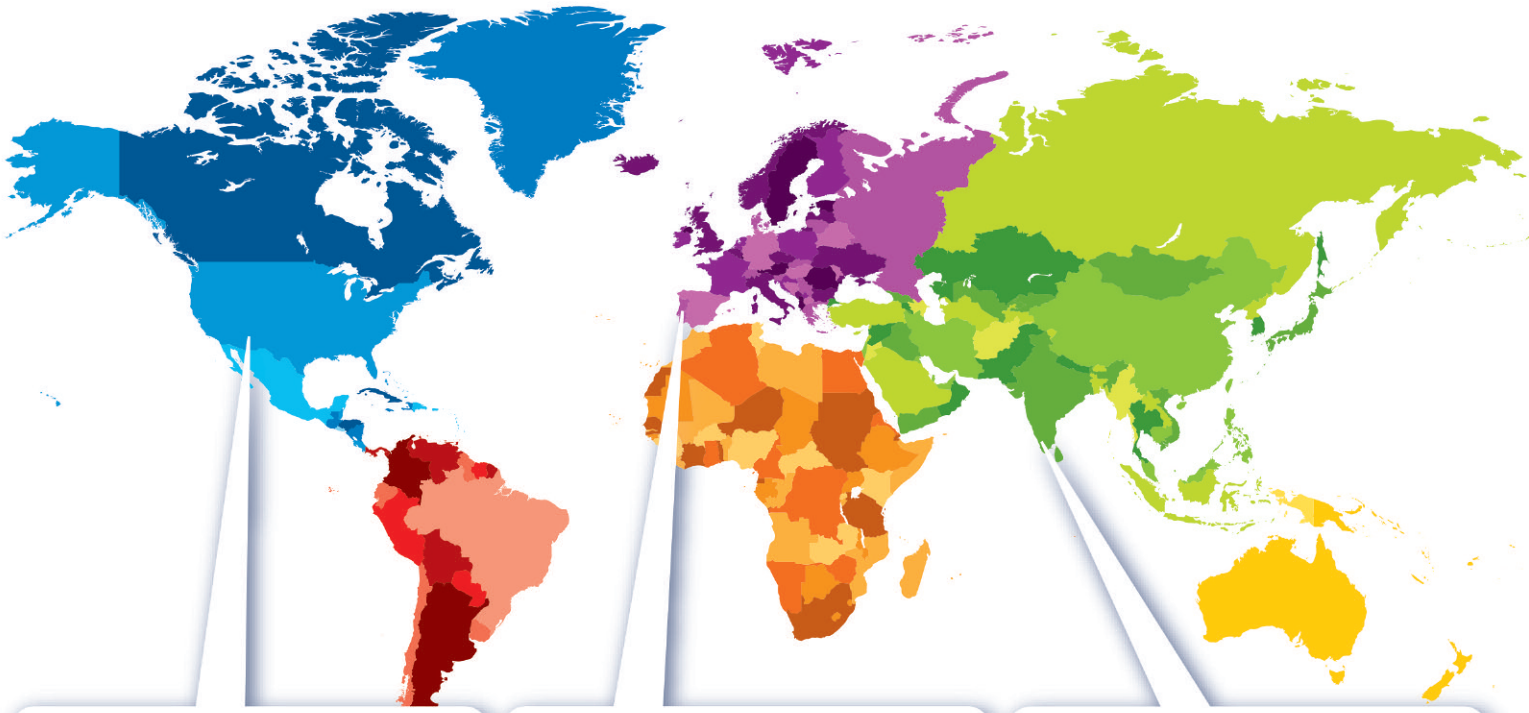

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DEVICE TRAINING

Maximizing Patient Adherence by Minimizing the Forgetting Curve

By: Chris Evans

INTRODUCTION

Imagine this scenario: you just bought a new home and your mother teaches you how to maintain the chlorine levels in the pool, a fairly complicated task she says you should perform once a month. You watch as she goes through each step, and when she leaves that night, you think you feel prepared. Thirty days later, though, is a different story — you walk outside, stare blankly at the pool for a few minutes, then walk inside and call your mother.

We've all been in situations like this where someone teaches you to do something that's not a regular task. A day later, you're able to recall that information pretty easily. A week on, it's a little fuzzier. As time passes, the information fades more and more. This is called the forgetting curve. Research dating back to the late 1800s shows that as time passes, less and less information is retained.[1]

Forgetting is probably OK when it comes to pool maintenance, but now imagine you have just been diagnosed with a chronic condition such as diabetes and the complicated task you need to perform is self-administering a dose of injectable medicine in your home, miles away from a medical professional.

In this situation, there is little room for error. There are other factors at play in addition to the forgetting curve, including the fact that the patient is not just tasked with the physical aspect of learning how to operate a new drug delivery system, but also the psychological reality that their lives are likely forever changed based on their recent diagnosis.

For these reasons, combined with a trend toward patients demanding treatment solutions they can self-administer outside of clinical environments, it is important that pharmaceutical companies and their drug delivery system partners proactively address the forgetting curve by rethinking how patients learn to use self-administration systems.

FIGURE 1

Connecting self-injection delivery systems, such as West's SmartDose injector, with training, education, and rewards on a device such as a smart phone may help increase adherence and improve patient outcomes.

PUTTING PATIENTS FIRST

Being diagnosed with a chronic condition is not easy. With diseases such as diabetes, hemophilia, rheumatoid arthritis, and multiple sclerosis and other chronic conditions, a patient is often beginning a life-long journey of care. After the initial shock of diagnosis has worn off, patients may experience a sense of relief that the cause of their health issues has been found. But many will respond with deep-seated emotions, such as anger or depression. The

need to adhere to a regimen of treatment may be met with denial, fear, or anxiety.

While adjusting to their new normal, patients around the world with chronic diseases are also seeking freedom from frequent doctors' visits, sometimes opting instead to self-administer their critical medications at home, when offered. This trend is emerging alongside another: an increase in new biologic and biosimilar medicines for the treatment of many autoimmune diseases.

With a steady pipeline of biologics and biosimilars poised to come onto the market as self-injectable treatments for many chronic conditions – often in auto-injectors or wearable injector systems – the pharmaceutical industry is experiencing the very beginning of the potential that exists for a new wave of drug delivery. Patients who must regularly self-administer medication have eagerly awaited this shift to more user-friendly drug delivery systems that better align with how they live their everyday lives.

However, as the use of biologic therapies is on the rise, it can be challenging for patients tasked with injecting these therapies to do so consistently and effectively, as many are delivered as large doses of highly viscous medicines. This is compounded by the fact that biologics are often dosed less frequently, meaning that just as a patient is adjusting to a new diagnosis and how to use a self-administered therapy and new drug delivery system, the time between doses gets longer and potential loss of device familiarity looms larger. Knowing what we know about the forgetting curve, that poses a real problem for patients.

DEVELOPING FOR USABILITY

Before patients ever have a drug delivery system in their hands, manufacturers of that system need to understand the fundamentals of patient-centric design so they can create self-injection systems that patients can and will use. One of the most successful elements in fulfilling the need for patient-centric design is human factors analysis, which benefits the patient by making injection systems more comfortable and user-friendly. Human factors analysis accomplishes this through environmental research: observation and interviews provide the critical context needed to make a qualitative assessment of a patient's abilities and challenges. Observing patients as they go about their day — and considering all of the surrounding environmental factors such as temperature, ambient noise, and lighting — can help researchers better understand how the patient will use a self-administration system. In-person surveys, questionnaires, user-based performance testing, and heuristic analysis also add to the base of human factors knowledge.

By taking a systematic, data-driven human factors approach to addressing usability earlier in development of injectable drug delivery systems, it's possible to troubleshoot and eliminate or minimize the risk of potential user errors and help build successful outcomes for the end-user patient. Incorporating patient feedback earlier into the design process also assists in creating delivery systems that address factors such as reducing fear and discomfort during the injection process.

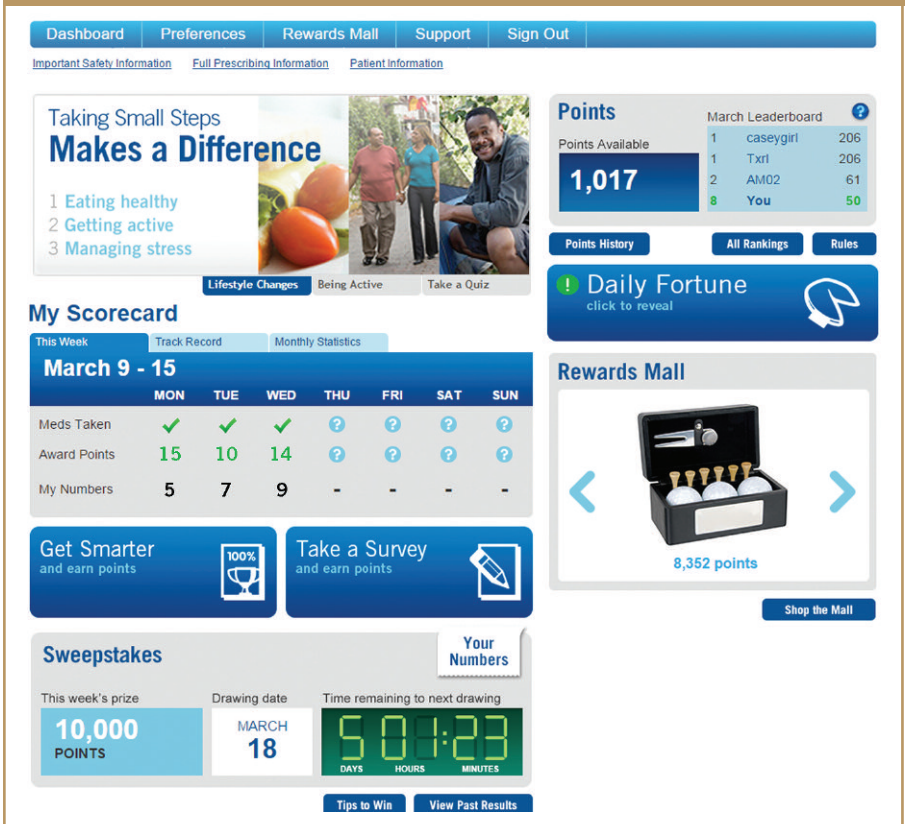
What does patient-centered design mean in practical terms? It includes listening to patients to address their personal priorities. Often, this involves talking to users three to five times before even prototyping a self-injection system to characterize their needs and how to best meet them. It also means understanding how patients feel about their diagnoses and conceptualizing how to make a drug delivery system that will improve their outlook, as well as finding out what features and design factors will improve medication adherence. It is also important to continually validate and improve designs to ensure that data-driven research is optimizing the approach to designing patient-friendly injectors. Armed with this knowledge, it's possible to create delivery systems that patients are more likely to use correctly the first time and every time.

SHIFTING THE FOCUS TO PATIENT TRAINING

No matter how well designed a delivery system is, however, a patient will still likely need some amount of training to become acclimated with proper use, instilling confidence and lowering anxiety. As the market for wearable drug delivery continues to expand, doses of biologic drugs are likely to get larger and trend toward less-frequent dosing will continue. As research on the forgetting curve shows, retention decreases the further out from a learning experience one gets, pharmaceutical companies and their drug delivery system manufacturing partners will need to equip patients with valuable training information that is more readily retained.

So, how do you make something stick in a patient's mind? The first answer is to make the training you provide to patients multisensory, meaning that more than one sense is activated during the process. Research shows that activating multiple senses during a training helps people internalize

FIGURE 2



Providing an online dashboard featuring at-a-glance education, training, and rewards creates an ecosystem that will help patients adhere to, and receive, insight regarding their therapeutic regimens.

that training and reduces the effect of the forgetting curve.[2] For example, if you hear someone reading the Instructions for Use (IFU) of a medicine while you're reading the IFU, that training is both audible and visual. If you're touching a device while you hear someone read the IFU, and the device itself speaks instructions to you, now the training is tactile, visual, and audible.

To begin to implement this style of training into West's self-injection systems, in 2016, West partnered with Noble®, a leader in patient-centric onboarding and training, to provide a multisensory-based educational training program. Studies report that 40% to 60% of patients could not correctly report what their physicians expected of them 10 to 80 minutes after they were provided with the information. In addition, more than 60% of patients interviewed immediately after visiting their doctors misunderstood the directions regarding prescribed medications.[3] By offering pharmaceutical companies multisensory education programs and technologies for wearable self-injectors, informed by human factors analysis into the development of patient training technologies and education materials, West and Noble aim to help improve the patient experience, reduce errors and anxiety, and help increase adherence to prescribed injectable therapies.

TAKING TRAINING TO THE NEXT LEVEL

Everybody involved in manufacturing, packaging, and delivering a medication to patients wants to achieve optimal patient outcomes. But, a key factor in this is ensuring patients comply with their treatment regimens, which can sometimes be difficult to achieve. Medication non-adherence is a leading cause of poor clinical outcomes and increased healthcare costs. Industry analysts estimate poor medication adherence costs the US healthcare system more than $290 billion in otherwise avoidable medical spending.[4] According to a study performed by Capgemini, the pharmaceutical industry's global revenue loss due to non-adherence to medication for chronic conditions is estimated to be $564 billion.[5]

Part of improving adherence comes through designing a user-friendly product based on human factors research and analysis, as previously mentioned. But training plays a critical role as well because it sets a foundation for ease of use of the product.

In the near future, training will meet people where they are spending more and more time: on their smart phones. An app may present visual confirmation of the steps, provide error correction, and offer multiple training events (instead of only one at the onset) that a patient can watch and re-watch as needed. Creating multiple touchpoints over the course of the 30 or 60 days patients are waiting between doses that activate different senses can help make patients feel more confident in self-administering their medication. One touchpoint may be a text message. Another, a conversation with a chat bot. Yet another, on-demand videos or picture glossaries stored in a digital library full of assets available at the touch of a screen.

A final improvement to the training space is making it part of a connected health experience. With an eye toward patient-centricity, West collaborated with HealthPrize® Technologies, LLC, to integrate their Software-as-a-Service medication adherence and patient-engagement

platform with West's injectable drug delivery systems (Figure 1). The combined offering provides electronically connected drug delivery systems that track when patients take their medication, educate and engage patients to help increase adherence and medical literacy, and reward them for compliance with their prescribed regimen (Figure 2). In short, they offer connected health.

Expanding that offering and applying it to training activities can be powerful. The software platform can serve as the backbone for the aforementioned digital library of training materials. Patients can receive points redeemable for real merchandise by chatting with someone or watching an on-demand video. If effective training on a drug delivery system takes 20 minutes, incentivizing patients to invest that 20 minutes can offer one more step toward the goal of maximum adherence. Going forward, biotech and pharmaceutical companies will likely look toward their drug delivery system partners for insights on training.

CHALLENGES WITH TRAINING

While the benefits to effective training have huge potential, there are a number of challenges presented as well. First and foremost, as with many things, is cost. Including multisensory training that is available in a digital library will come with increased expenses, which, in a world of shrinking reimbursements, could impact the bottom line for pharmaceutical manufacturers. As time passes and the market continues to become more patient-centric, this may change and the investment may be clearer.

Another challenge is a lack of data connecting increased adherence with improved outcomes. There is plenty of data showing that connected health solutions as well as direct education to doctors in areas with low medication adherence can help improve adherence levels. For example, patients enrolled in HealthPrize programs demonstrate persistently high engagement rates and materially higher adherence rates, nearly 50% higher than baseline, on average. In order to connect that higher adherence with improved outcomes, patient utilization needs to be monitored in the short-, middle-, and long-term and compared against ongoing patient health. That is something that is in its infancy. But things are changing. Just recently, biotech company Amgen and health and well-being company Humana partnered to identify opportunities to improve health outcomes by following patients who have five major diseases – cardiovascular disease, osteoporosis, neurologic disorders, inflammatory diseases, and cancer. The partnership will probe into specific therapeutic areas, one of which will be the impact of wearable technologies on medication adherence for these diseases.

SUMMARY

The markets for wearable drug delivery systems and biologics are expected to continue growing for many years. These trends, combined with a patient population that is looking for increased convenience and autonomy, place a mandate on pharmaceutical companies and their drug delivery system partners to improve training practices for patients beginning to learn to use self-injections systems. As the forgetting curve shows, retention drops as time passes. Therefore, employing research-backed methods such as using multisensory training materials will be important to consider. To that end, pharmaceutical companies should work with their drug delivery system manufacturers to make human factors-based, multisensory training a core part of their integrated drug solution. After all, it's the patients who will benefit, and that achieves a goal shared by all involved.◆

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BIOGRAPHY

Chris Evans is Vice President, Global Innovation, at West Pharmaceutical Services, Inc. He has been in product development for over 20 years, primarily in healthcare packaging and device development. He graduated from the University of Maryland with a degree in Biology/Chemistry, and his first decade of work concentrated on the manufacturing, engineering, and commercialization of new products working for various OEMs and design firms. Since then, he has worked mostly on the "front-end" of innovation, managing teams in discovery/user research, human-factors, mechanical innovation, concept creation, and intellectual property development. He is the holder of 19 US patents with several more pending. With West for 9 years, Mr. Evans is now responsible for transformational new product and technology development, focusing on device usability and enhancing the patient experience. He also manages West's Connected Health Initiative and the resulting partnerships and alliances brought together to assemble a "patient-engagement ecosystem."

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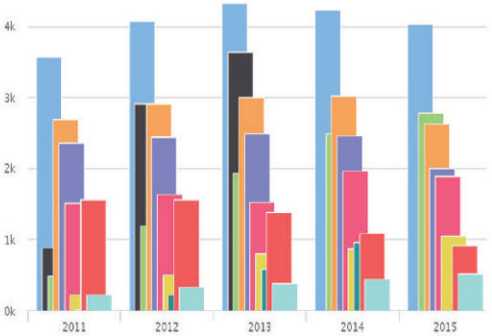

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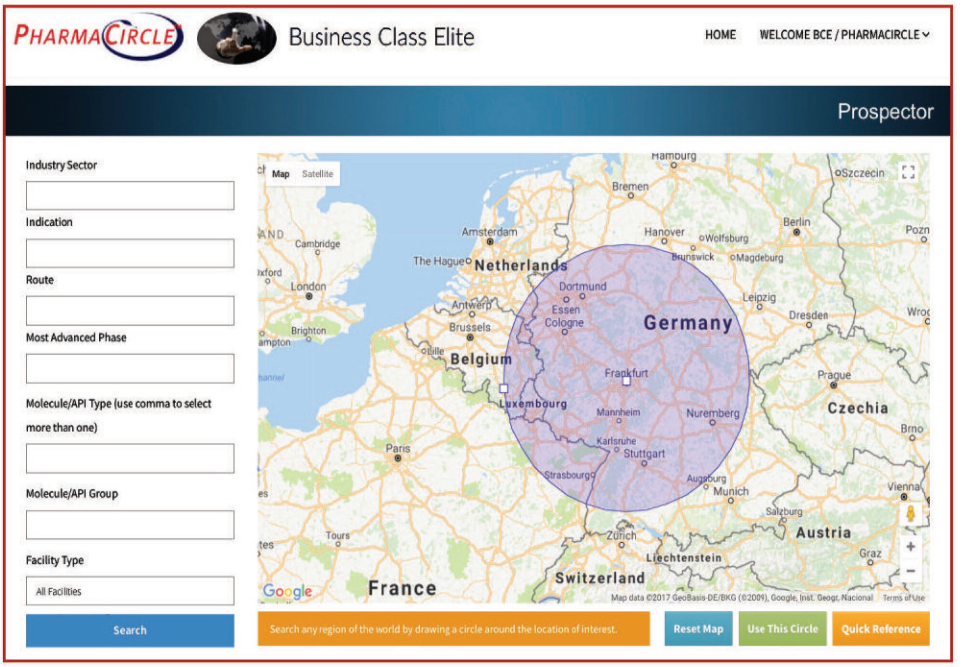

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INTRABODY DELIVERY

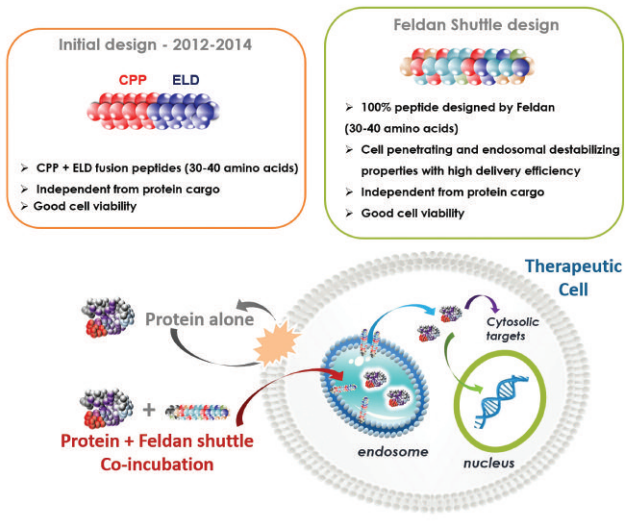
The Feldan Shuttle Technology: A Peptide-Based Method to Deliver Antibodies

By: Thomas Del'Guidice, PhD, Nancy Messier, PhD, and David Guay, PhD

INTRODUCTION

Throughout the past decade, the use of monoclonal antibodies and antibody-related products invaded drug market with billion-dollar sale blockbusters (eg, Humira, Alirocumab, Evolocumab), which reflects their great therapeutic potential for human therapies.[1-3] The number of biopharmaceutical antibodies in clinical drug development in 2015 increased 36% compared to 2014, with 53 novel products approved in Europe and the US for Phase 3 studies. Approximately 210 novel therapeutic antibodies are evaluated in the two earlier phases of clinical development to cure illnesses like asthma, multiple myeloma, Alzheimer's disease, and psoriasis.[4] While current antibody-based therapies aim at extracellular and transmembrane proteins, reaching the interior of cells with antibodies is still an interesting market to be explored because 60% of drug targets are believed to be intracellular. Indeed, there are many examples of intracellular proteins from nucleus, cytoplasm, and organelles (mitochondria, lysosomes, endoplasmic reticulum), which are suspected to be involved in disorders like oncogenic, autoimmune, and degenerative diseases.[5] The therapeutic potential of antibodies with intracellular targets ("intrabodies") was demonstrated with the insertion of coding DNA in mammalian cells that forced the expression of antibodies followed by the successful inhibition of cellular functions.[6] However, the intracellular DNA expression of functional antibodies by mammalian cells is laborious and hard to translate to clinical applications. The direct delivery of intrabodies as proteins could become therapeutically interesting to specifically target signaling cascade components and to mediate instantaneous biological effects.[5] However, the lack of safe and robust protein delivery protocols slows down the transfer of intrabodies toward widespread clinical use.[5,7] In this review, we present the Feldan Shuttle technology, a peptide-based delivery method, that could provide the efficient and safe intrabody delivery in mammalian cells.

FIGURE 1

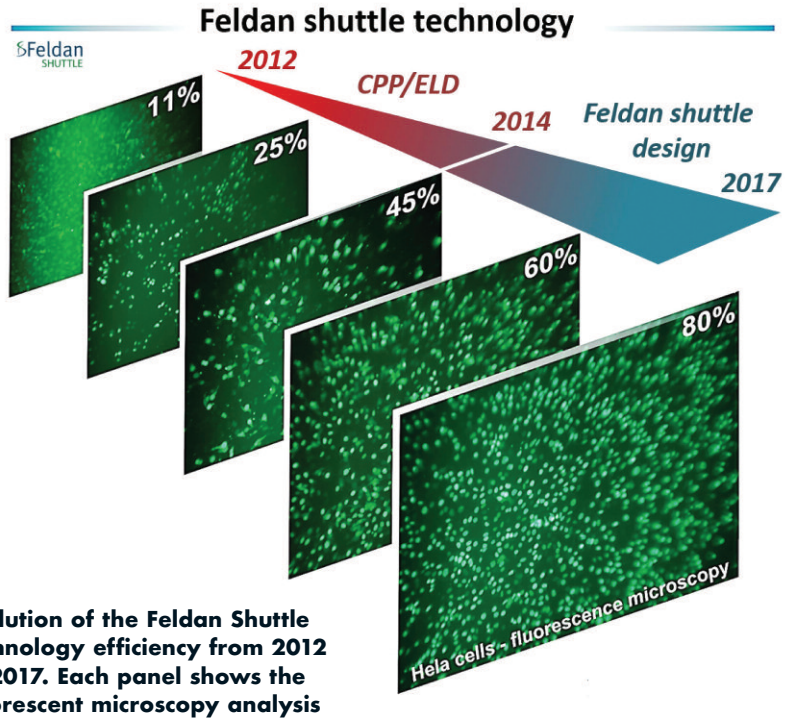


Schematic representations of the Feldan Shuttle technology from 2012 to 2017 (upper panels), and of intracellular transport pathway inside therapeutic cells (bottom panel). The Feldan Shuttle technology provides the efficient and safe internalization followed by endosomal escape of functional antibodies via a simple co-incubation protocol.

ADVANTAGES OF INTRABODIES OVER OTHERS PROTEIN CARGOES

The use of intrabodies as therapeutic molecules brings solutions to overcome challenges currently faced by the pharmaceutical industry with small molecules and antibodies targeting extracellular substrates. An antibody has the advantage, over classical small molecule drugs, to be highly specific for a single protein. They can be designed to discriminate between splice protein variants and even post-translational subpopulation (eg, a phosphorylated protein).[6] This high level of specificity is accessible by using antibody fragments like antigen-binding fragments (Fabs) and single-chain variable fragments (scFvs). With the exponential growth of the therapeutic monoclonal antibody market, the technologies to design and produce antibodies enable antibody manufacturing scale up and are clinically approved. Clinical trials show that antibodies, which can be recombinantly produced and humanized, are generally well-tolerated and have high substrate specificity that significantly reduce the risk of deleterious side-effects compared to many others types of therapeutic products.[3] Obviously, intrabodies opens new therapeutic avenues by their capability to bind intracellular proteins, which cannot be modulated by conventional antibodies or chemical drugs. The immediate but transient blocking effect of the targeted protein by intrabodies also provides an advantage over more indirect and less-specific RNA interference technologies or permanent modification provided by CRISPR nucleases.[6]

FIGURE 2



Evolution of the Feldan Shuttle technology efficiency from 2012 to 2017. Each panel shows the fluorescent microscopy analysis of the intracellular delivery of a recombinant GFP fused to a NLS (Nuclear Localization Signal) in HeLa cells with the Feldan Shuttle technology. Values indicate the % of cells with a nuclear GFP signal (cell viability 90%-95%).

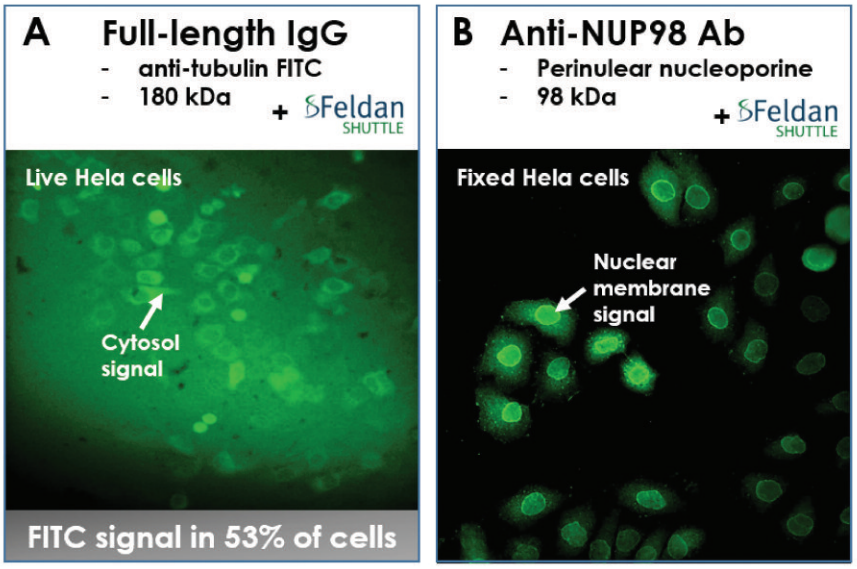
THE INTRABODIES DELIVERY CHALLENGE

Usually, proteins, including antibodies, do not have the innate capacity to penetrate cells by themselves in sufficient therapeutic concentration. Unfortunately, current viral and non-viral delivery methods (inactive virus, electroporation, chemical agents) have mainly been developed to introduce foreign genetic material but are poorly efficient to directly deliver proteins in cells, leaving few options for the delivery of purified antibody.[8] Since antibodies engineering is a laborious process, especially to produce a specific and humanized monoclonal antibody, making intrabodies the new generation of therapeutics requires pressing and robust delivery methods well tolerated by mammalian cells and clinically acceptable.[9]

BRIEF REVIEW OF INTRABODIES DELIVERY INVESTIGATIONS

The feasibility of targeting intracellular proteins using intrabodies has been proven using either intracellular overexpression of antibody fragments through a gene-based approach or microinjection.[10] In parallel, a few academic teams reported the use of electroporation to deliver antibodies.[11] Even if electroporation could potentially be a relevant delivery method, this process is not efficiently applicable to *in vivo* therapeutic applications and notoriously leads to high mortality in many cell types. Few corporate and academic groups also reported that some cationic lipid agents could be used to translocate antibodies, but the toxicity associated with their use prohibits their transfer in clinical trials for both ex vivo and *in vivo* studies.[12,13] Other protein-delivery techniques

FIGURE 3A&B



Intracellular delivery of antibodies with the Feldan Shuttle technology. Figure 3A shows live cell imaging after the delivery of a FITC anti-tubulin antibody with the Feldan Shuttle technology. Figure 3B shows immunolabelling of a perinuclear protein nucleoporin with an anti-NUP98 antibody delivered with the Feldan Shuttle in HeLa cells. Functional antibody delivery was visualized by fluorescence microscopy (20x).

have been recently developed and could potentially be applied to intrabodies. For example, the use of a vector-free microfluidic platform to mediate physical force that "squeezes" cell membrane and leads to cell poration and passive protein uptake.[14] In parallel, some laboratories modified the structure of antibodies to design engineered therapeutic antibodies in order to promote self-delivery, but the method is complex, requires important know-how, limits high throughput screening, and could influence the activity of the modified intrabodies.[2] The following describes the Feldan Shuttle peptide-based technology as a robust method to enable quick and easy delivery of intrabodies in cells for both functional screening processes and therapeutic strategies.

THE FELDAN SHUTTLE TECHNOLOGY

Cell-Penetrating Peptides as Intrabody Carriers

Using short protein domains as intracellular carriers is a strategy discovered in 1965 that was rationally considered 30 years ago after the identification of the first cell-penetrating peptide (CPP), isolated from the HIV-transactivator TAT.[15,16] Actually, several CPPs have been identified and fused to proteins to mediate their intracellular delivery. However, CPPs mediate intracellular uptake through endocytic processes that lead to the sequestration and the enzymatic degradation of proteins into vesicular compartments, named endosomes, that substantially reduces the likelihood to get functional effect.[17]

The Endosomal Escape Strategy

Indeed, the endosomal escape of delivered proteins is a challenging and limiting step that requires endosome destabilizing strategies.[18] To overcome this hurdle, peptides with endosomal leakage properties could promote the cytosolic release of biomolecules from endosomes.[19,20] These peptides, named endosomal leakage domains (ELDs), are unable to deliver proteins in cells on their own. Indeed, using both CPPs and ELDs could be an approach resulting in a peptide with both protein uptake and endosomal escape properties (Figure 1). Recently, the fusion of CPPs with ELDs was validated as a promising peptide-based delivery strategy with easily adaptable protocols for macromolecule delivery that provided exciting results into mammalian cells.[21-23] These investigations encouraged us to deepen our understanding of the biochemical and structural properties required for the design of peptides mediating the efficient and safe delivery of proteins into mammalian cells.

Toward a New Generation of Intrabody Carriers

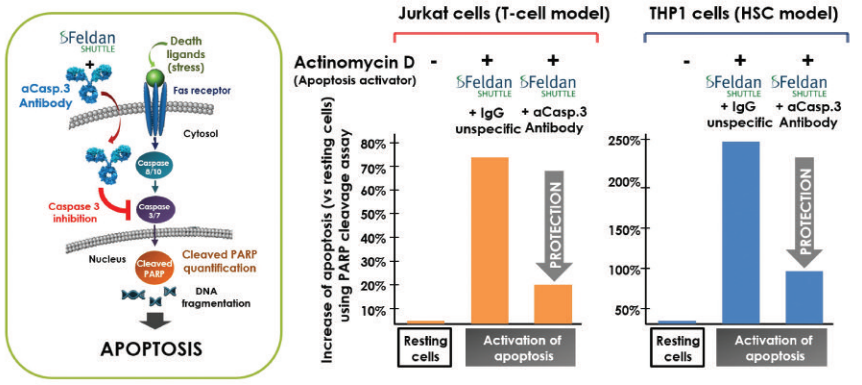
The research division of Feldan aims at developing and patenting a new generation of peptides named Feldan Shuttles that provides the efficient, safe, and fast intracellular delivery of proteins, like antibodies, in several mammalian cells, including human stem cells, lymphocytes, myeloma, and primary cells. Initially based on the fusion of natural CPPs and ELDs sequences, Feldan peptides are now rationally designed and optimized for the delivery of intrabodies in living cells (Figures 1 & 2). Exempt from chemical modifications, the Feldan Shuttle is degraded after transient active use, a characteristic

that considerably decreases regulatory burdens for human applications. Feldan Shuttle technology opens new avenues allowing the modification of hard-to-transfect cells with high therapeutic potential. These easily soluble designed peptides can deliver diverse antibodies in the cytoplasm of adherent and suspension cells using a simple co-incubation protocol. The Feldan Shuttles offer a high level of adjustment and accuracy to reach functional effects in cells. Indeed, this technology is in continuous improvement using both sequence analysis and computational learning approaches. Thereby, the Feldan Shuttle is a promising and effective peptide-based alternative to safely bring antibodies and other proteins in the cytoplasm of cells. Our main objective is to use the Feldan Shuttle platform to develop a high throughput technology that will bring a new strategy to target intracellular epitopes and to modulate signalling pathways, enabling the use of intrabodies as a drug to prevent, treat, or cure diseases.

INTRABODIES DELIVERY WITH THE FELDAN SHUTTLE TECHNOLOGY

Initial results using the Feldan Shuttle demonstrates that intrabodies can be internalized while keeping their ability to bind a specific target to mediate cellular activity. The experiments presented in this review show that the Feldan Shuttle efficiently delivered the following functional antibodies: an anti-tubulin antibody (Figure 3A), an anti-NUP98 antibody that label the perinuclear protein nucleoporin (Figure 3B), and most importantly, two anti-Active Caspase 3 monoclonal and polyclonal antibodies that bind and inactivate the pro-apoptotic Caspase 3 protein in human monocyte THP1 and human immortalized CD4 T lymphocyte Jurkat (Figure 4).

FIGURE 4



Anti-apoptosis assay with Feldan Shuttle-mediated anti-Caspase 3 delivery. Left panel shows a schematic representation of apoptotic signalling cascade and the inhibition of the PARP cleavage by an anti-Caspase 3 antibody. The graph shows the results of a monoclonal (mAb) and a polyclonal (pAb) anti-Active Caspase 3 antibody transduction efficiency in Jurkat and THP1 cells, respectively. Each antibody cargo protein was individually co-incubated with the Feldan Shuttle, prior to being exposed to THP1 or Jurkat cells.

Results in THP1 and in Jurkat cells showed that the Feldan Shuttle technology efficiently delivered the functional anti-Active Caspase 3 antibodies. Anti-TNF antibody was used as a non-specific IgG negative control, and cleavage of PARP protein was used as apoptosis measurement. In presence of the cytotoxic inducer actinomycin D, the Feldan Shuttle-mediated delivery of each anti-Active Caspase 3 monoclonal (mAb) and polyclonal (pAb) antibodies in THP1 and Jurkat cells, respectively, resulted in cell protective effect via the reduction of the basal level of apoptosis compared to the non-specific IgG antibody control condition. The simple and adaptable co-incubation protocol used here present many advantages to preserve cells from toxicity. Indeed, the Feldan Shuttle and each antibody were co-incubated with adherent or suspension cells only for 1 to 10 minutes, illustrating the fast delivery action mode of the technology. These results confirmed that the Feldan Shuttle technology efficiently and safely delivers functional intrabodies in mammalian cells.

FELDAN SHUTTLE TECHNOLOGY: APPLICATIONS & PARTNERSHIPS

Because the vast majority of therapeutic antibodies still aim at extracellular targets, the implementation of the Feldan Shuttle technology to deliver intrabodies in mammalian cells provides huge interests in the antibody market. The development of a Feldan Shuttle platform for the screening of functional intrabodies should result in the identification of intracellular protein targets with therapeutic interest. In the development process, multiple antibodies need to be generated against one target and subsequently screened for their specificity. Furthermore, this peptide-based strategy could be an alternative to optimize the use of small drug delivery molecules developed by industry/biopharmaceutical research that fail to localize therapeutically

relevant protein-protein interactions inside the cell. The access to high-quality intrabodies will also allow Feldan Therapeutics to transiently modulate the cell machinery to get functional changes. Moreover, the Feldan Shuttle technology could deliver engineered intrabodies to transiently modulate signaling pathways at different cell cycle stages during cell proliferation and differentiation. This may be achieved with the delivery of specific intrabodies that could trap protein targets into specific intracellular compartments.[5] For example, the intrabody-mediated transport of proteins into the nucleus could induce the specific and direct modulation of genome expression.[6] The easy manipulation of this soluble and degradable peptide product could also be used for treatments requiring narrow time windows to protect brittle cells from toxic long-term exposure, and treatments requiring extended intrabody delivery to mediate more sustained biological effects.

The use of the Feldan Shuttle Technology for intrabody delivery can be directly used for ex vivo manipulation of mammalian cells to support the development of the screening platform. Its low cost of manufacturing, ease of use, and innocuity also provide this tractable method toward an industrial platform for the development of topical therapeutic products and local injections of intrabodies to treat problematics like skin inflammation in psoriasis, pain in osteoarthritis, and neovascular age-related macular degeneration.[4] Because the in vivo delivery of intrabodies remains the ultimate goal for drug development, Feldan Therapeutics performed preliminary *in vivo* investigations with local injections of diverse recombinant proteins with the Feldan Shuttle in the brain and the muscle of rodents. Injected proteins diffused in tissues and provided functional activity, indicating the potential of this technology for *in vivo* applications. However, given the more complex environment, the systemic injection of the Feldan Shuttle product is still limited and needs improvements with peptide protection strategies like the use of peptide-coating agents and non-permanent peptide-cargo linking strategies. In this regard, Feldan Therapeutics continuously develops partnerships to seize exciting opportunities and expertise to combine the Feldan Shuttle technology with other approaches and to raise it toward intrabody-based clinical applications. ◆

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BIOGRAPHIES

Dr. Thomas Del'Guidice is a Research Specialist at Feldan Therapeutics. His work focuses on the development of the Feldan Shuttle, a peptide-based technology for the intracellular delivery of native and engineered proteins. He earned his PhD in Molecular and Cognitive Neurobiology from the Laval University, Québec-Canada. He achieved an industrial post-doctoral fellowship at Feldan Therapeutics in the design and the screening of peptide sequences for the intracellular delivery of recombinant proteins and drug reagents in mammalian cells.

Dr. Nancy Messier is a Development Director at Feldan Therapeutics. She earned her PhD in Microbiology from the Laval University, Québec-Canada for her research on the implication of the class 1 integrase structure-function in bacterial antibiotic resistance. She has more than 10 years of expertise in the analysis and the production of recombinant proteins and leads the development of the intrabody delivery project at Feldan Therapeutics.

Dr. David Guay is Research Director at Feldan Therapeutics. He earned his PhD in Molecular and Cell Biology from Laval University, Québec-Canada for his research on the implication of a transcription factor in DNA repair and chemotherapy-resistance mechanisms. He held a post-doctoral fellowship from McGill University in chemical engineering, where he developed a DNA delivery technique based on a non-thermal plasma technology. His research at Feldan Therapeutics focuses on the Feldan Shuttle, a peptide-based technology designed to deliver native proteins, namely antibodies and CRISPR nucleases, in therapeutic cells.

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FOAMED SILICONE

Molded Porous Silicone for Delivery of Macromolecules & Low-Solubility APIs

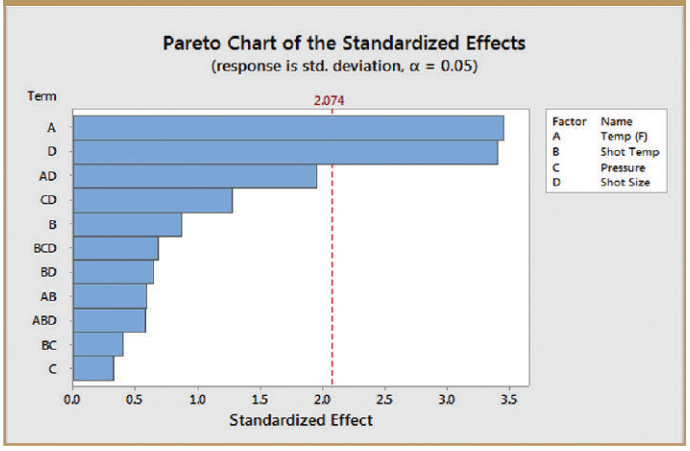
By: James Arps, PhD, and Matt Petersen, PhD

INTRODUCTION

Drug delivery systems are generally designed to provide therapeutic amounts of active pharmaceutical ingredient to the proper site in the body over an acceptable period of time as quickly and safely as possible. Implantable drug delivery systems offer several advantages over conventional oral or parenteral dosage forms. First, implantable devices can allow site-specific drug administration where the drug is most needed. This may also allow for significantly lower systemic doses of drug that can minimize potential side effects. Second, implantable devices allow for sustained release of a therapeutic agent for months to years from a single device. The last and perhaps most important advantage is patient compliance, as the treatment regimen associated with an implantable device is generally simpler and less onerous than pills or injections and proceeds without patient intervention. Further, if the device is made of a durable resin, treatment can be discontinued if necessary or desired. Many of these drug delivery systems are polymer-based, with notable examples including subcutaneous implants based on ethylene vinyl acetate for treatment of opioid abuse, steroid-eluting PLGA ophthalmic implants for the treatment of macular edema, and silicone vaginal rings used in hormone replacement therapy.

While their rapid uptake in the market shows great versatility, existing approaches and materials have major limitations. In applications requiring delivery of a poorly bioavailable or sparingly soluble drug, the low surface area presented by a conventional polymer matrix can limit dissolution and drug release. At high drug loadings or when drugs are encapsulated that might contain interfering chemistries, the polymer matrix can be disrupted, leading to a loss of mechanical integrity. Finally, in many cases, the mechanical shear or temperature associated with typical polymer processing conditions can have a negative effect on sensitive drugs if they are incorporated prior to molding or extrusion of the implant.

FIGURE 1



These issues are especially acute when the delivery of large-molecule therapeutic agents, such as proteins, antibodies, and nucleic acids, are desired. For conventional devices, biologically relevant large molecules (molecular weight larger than 1 kDa) often have minimal solubility in the polymer matrix and extremely slow diffusion. As a result, release is slow or practically non-existent. Further, for many biomolecules, even modest process temperatures greatly increase the likelihood of degrading peptides or denaturing proteins. The ability to controllably release high concentrations of macromolecules over an extended period of time from a mild, manufacturable system is a "holy grail" in controlled release.

THE PROMISE OF POROUS SILICONES

Silicone is well-established as an implantable device material for controlled delivery of a wide range of drugs due to its biocompatibility, chemical inertness, capacity for controlled release, and amenability to formation into a range of geometries by such techniques as molding and extrusion. In contrast to thermoplastics, such processing is often possible at relatively low temperatures (eg, 100°C or less). Since many modern silicone formulations are viscous fluids at room temperature, incorporation of actives ahead of molding can be achieved with minimal heat load and shear compared to extrusion and forming approaches used for thermoplastics. Following introduction into the body drug dissolves in the matrix, diffuses to the surface, and into the fluid surrounding the implantation site. By appropriate selection of formulation "handles," such as material composition, drug formulation, device geometry, drug load, and/or incorporation of rate-limiting or enhancing excipients, silicone devices can be fashioned in such a way as to gradually and predictably release drugs over extended time periods.

In contrast to conventional monoliths, the use of microporous carriers in drug delivery has been explored in various osmotic drug delivery systems with promising results. By introducing pores into the silicone system, the existing approaches to control drug release can be expanded to address liquid penetration into and subsequent elution from porous materials. Appropriate formulation and processing of the material can control the flow behavior of the fluid into the matrix itself, rather than allowing access to only the outer surface of the device. This can significantly impact the dissolution kinetics of the drug compared to existing approaches. In addition to existing methods for controlling release properties, the formulator can also control such properties of the porous implant as pore size, tortuosity, percolation, and wettability.

In contrast to monoliths, when a porous hydrophobic polymeric drug delivery system is placed in contact with the appropriate dissolution medium, release of drug into the medium is accompanied by swelling of pores and drug dissolution in the water-filled pores or from surface and by diffusion through the fluid-filled network. Depending on the interplay between these factors, drug release from a porous carrier may be complete within 10 minutes or be incomplete after several hours or days.

ProMed has developed several means of incorporating APIs into porous, high surface area silicone foams. This novel approach allows incorporation of much higher loads of previously problematic drugs, including low-solubility and large-

FIGURE 2

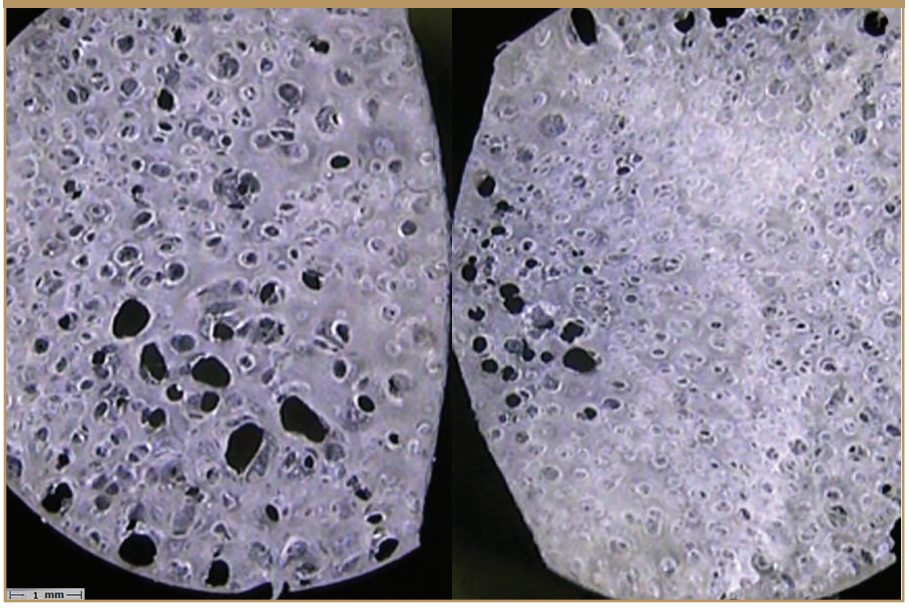
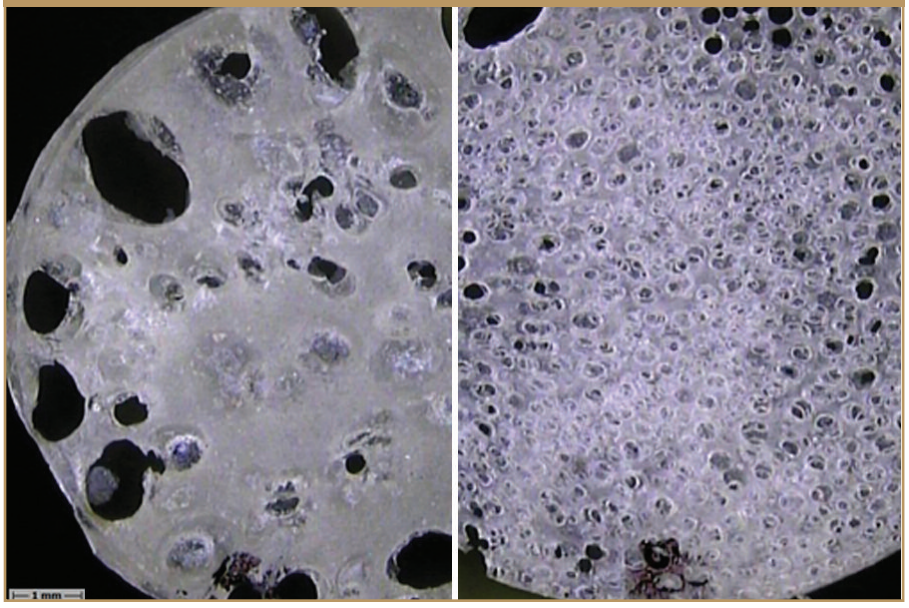


FIGURE 3



"A key advantage of Silbione foams is their ability to cure at low temperatures, typically between room temperature and 60°C over several minutes, which minimizes risk of API degradation. By utilizing a chemistry capable of generating a pore-forming gas instead of foaming agents that may not completely volatilize during the curing process, it is possible to create highly biocompatible porous implants that can be loaded with very high drug doses while not substantially compromising mechanical integrity and avoiding medically undesirable byproducts."

molecule APIs, control over their release, and potential enhancements to drug bioavailability while using equipment and procedures widely used for silicone molding and processing of pharmaceutical dosage forms at commercial scales.

MATERIALS & MANUFACTURING APPROACHES

Silbione® RT foams (Bluestar Silicones) are biocompatible two-component low-viscosity materials that combine low density with excellent mechanical properties. Once part A and part B are mixed, the silicone elastomers crosslink via a polyaddition reaction, and hydrogen gas is evolved to promote void formation. A key advantage of Silbione foams is their ability to cure at low temperatures, typically between room temperature and 60°C over several minutes, which minimizes risk of API degradation. By utilizing a chemistry capable of generating a pore-forming gas instead of foaming agents that may not completely volatilize during the curing process, it is possible to create highly biocompatible porous implants that can be loaded with very high drug doses while not substantially compromising mechanical integrity and avoiding medically undesirable byproducts.

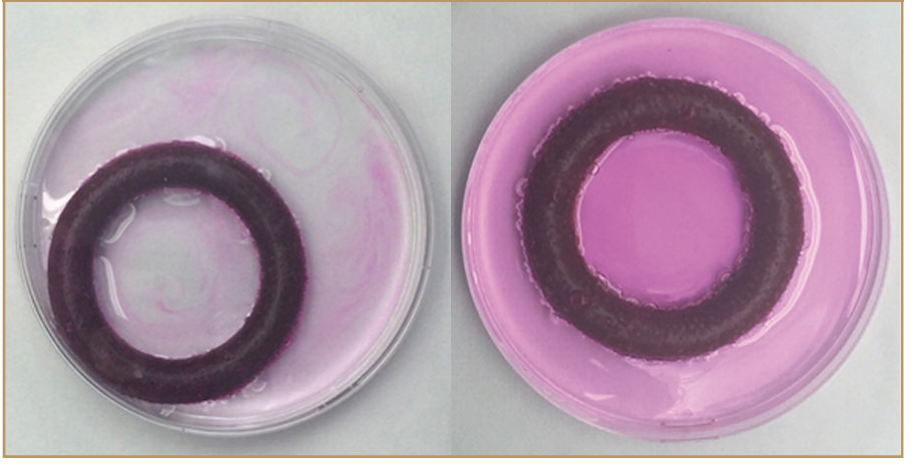
ProMed has identified and optimized critical processing parameters that impact the number, size, and shape of these voids as well as their interconnectedness. This understanding enables control of overall density, drug loading, and drug release by diffusion through both pores and the polymer matrix. Figure 1 shows the results of a two-factor design of experiments study used to understand the impact of key processing parameters on the foam microstructure. For a particular molding cavity geometry, the most important factors affecting pore size and connectivity were found to be molding temperature and shot size.

Figure 2 compares optical cross sections of two foams with similar average density but cured at lower and higher mold temperatures. At higher temperature, the cure time is reduced and pore size is modified as the silicone rapidly "sets" before the pores can combine with adjacent voids. Conversely, a smaller amount of silicone uniformly distributed through a fixed volume must effectively incorporate a higher void volume, resulting in a foam construct with lower average density. Figure 3 shows two representative lower and higher density foams cured at the same temperature.

USE AS A DRUG DELIVERY MATERIAL

Two important factors contributing to release of a drug form a porous content are the rate of water permeation into the matrix and the water solubility of the drug itself.

FIGURE 4

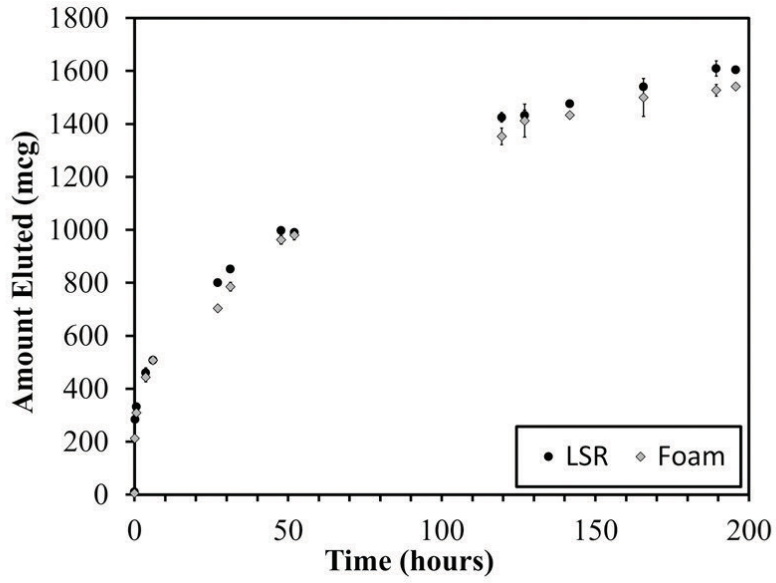


To explore these effects in porous silicone, a series of experiments were performed using several model compounds including Rhodamine B (hydrophilic small molecule LogP = 1.95, 479 g/mol), Ibuprofen (hydrophobic small molecule, LogP = 3.97, 206 g/mol) and Bovine serum albumin (BSA, large molecule 66.5 kg/mol).

Silicone intravaginal rings (IVRs) have been commercialized for contraception and hormone replacement therapy and are in development for prevention of HIV and the treatment of endometriosis. ProMed has significant experience developing IVRs. Here, one such geometry was used as a model device architecture. In an effort to compare the performance of fully dense IVRs with foam constructs, a 30-durometer medical-grade liquid silicone rubber (LSR) was premixed with Rhodamine B. Rings were molded via injection molding and weighed a day after molding to ensure cure and off-gassing was complete. Each ring had approximately 1.5 g of Rhodamine B and weighed approximately 10 g. For the foam rings, the rhodamine B was mixed into the B component of the two-part foam system and made using a similar transfer press procedure. Dimensions and drug loading were similar between foamed and unfoamed systems. Rings were then suspended in 1 L of deionized water. A small weight was attached to the bottom of each ring to keep it submerged. The rings were maintained at room temperature and stirred at 100 RPM. Samples for quantitation of elution were taken periodically, and concentration was determined using UV-VIS Spectrometry. Figure 4 shows a photo sequence of rhodamine diffusing from a foam ring in a simple petri dish over several days.

The high solubility of rhodamine is evidenced when the in vitro release of the fully dense and foam silicone IVRs are compared (Figure 5). The rates are nearly identical suggesting that porosity is a secondary factor in determining the release when diffusion and dissolution into surrounding media are not rate-controlling steps.

FIGURE 5



The release behavior, however, is quite different for the two materials when a more hydrophobic small molecule is utilized. Figure 6 compares the release of Ibuprofen in silicone foams with two different densities and the same percentage drug loading. Here, the effect of water ingress on drug release is much more apparent. A greater number of pores, or larger pores present with lower density foams, allow for more surface area for water to contact the drug. Incorporation of a dissolution enhancer, such as methyl cellulose, can further increase water uptake, pore interconnectedness, and the subsequent release rate of these more hydrophobic drugs.

Finally, release of a model protein,

FIGURE 6

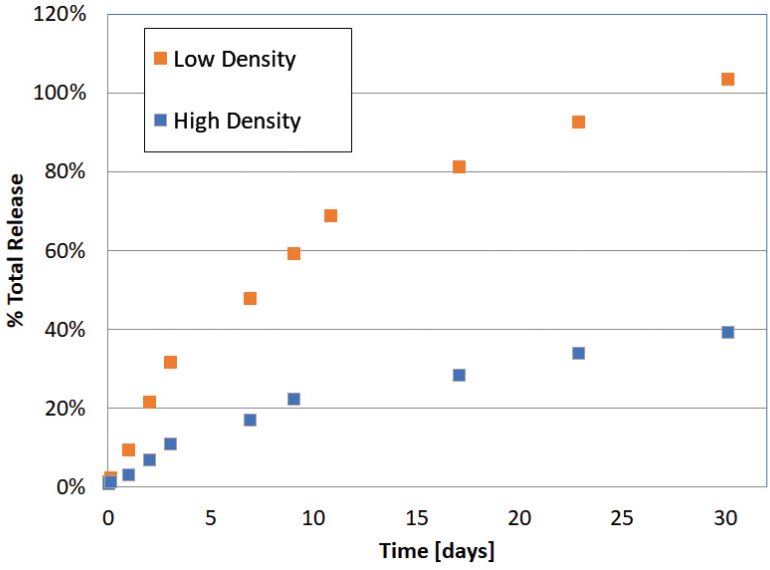
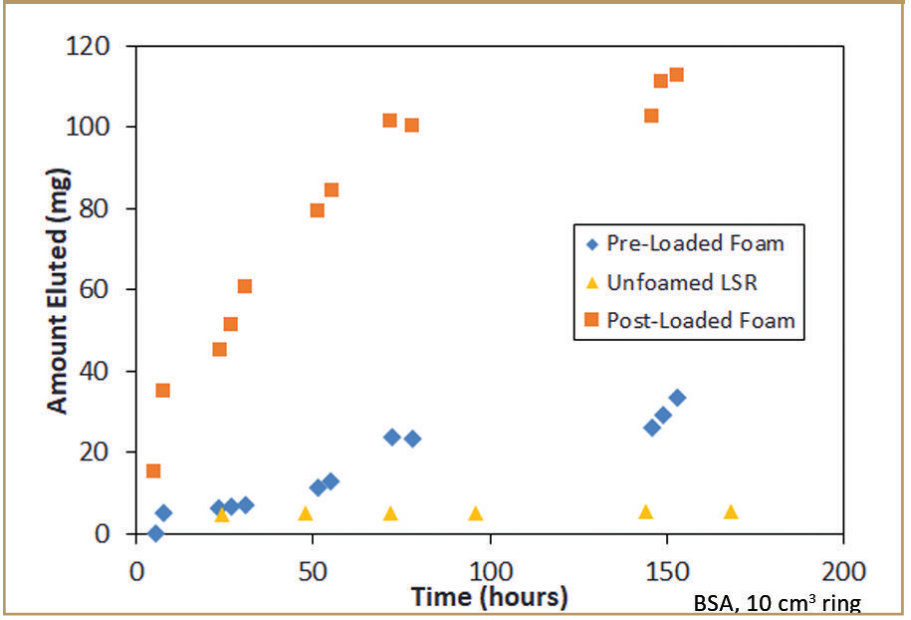


FIGURE 7



bovine serum albumin (BSA) was evaluated. Bovine serum albumin powder was mixed into silicone Part A and Part B at 0-25 wt%. A controlled quantity of both silicone parts was combined in a 1:1 ratio through a static mixer into a heated mold and cured. Additional samples were prepared by mixing BSA into liquid silicone rubber without use of a foaming agent and by soaking a preformed ring in a BSA solution followed by freeze drying. Release studies were run in phosphate acetate buffer and BSA elution was tracked by UV-Visible spectrophotometry.

BSA elution for the different preparation conditions is shown in Figure 7. For post-loaded foams burst release was observed from 0-72 h followed by much lower release rates. Pre-loaded BSA foams exhibited a slower but more linear release behavior while un-foamed fully dense silicone effectively binds the BSA within the matrix, completely blocking release. By controlling loading and ring pore volume through compounding and molding, facile control of water permeation and payload release rate is possible.

CONCLUSIONS

Foamed silicone is capable of sustained, controlled elution of hydrophobic small molecule and large macromolecular payloads. Drug release was demonstrated using a novel tunable, industrially scalable IVR platform with release kinetics similar to that of reservoir-type design by a simple matrix-type manufacturing route. By employing simple changes to processing parameters, hydration and release kinetics can be adjusted. By making linear, sustained release possible in an easily manufacturable construct, this approach could potentially expand the scope of drug delivery to include a rapidly emerging range of macromolecular therapeutics.◆

ACKNOWLEDGEMENT

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BIOGRAPHIES

Dr. James Arps is a Program Director at ProMed Pharma. He has over 15 years of experience managing product development and commercialization of medical devices, advanced coatings, and drug delivery technology. He has worked with industry and academic partners, guiding products through all stages of development from conceptualization through to commercial release. At ProMed Pharma, he oversees program development activities for polymer-based drug-releasing implants and combination device components. He earned his PhD in Applied Physics from Vanderbilt University and his MS in Management of Technology from the University of Texas-San Antonio.

Dr. Matt Petersen is a Principal Scientist at ProMed Pharma, where he is responsible for technical leadership in formulation and product development for drug-device combination products. His interests in controlled and sustained release include applications in women's health, ophthalmology, and prevention of HIV transmission using both established and emerging polymeric delivery systems. Dr. Petersen earned his PhD in Materials Science and Engineering from the University of Minnesota, Twin Cities on the subject of microstructured polymeric drug delivery vehicles for targeted drug delivery.

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SPECIAL FEATURE

Analytical Testing – Contractors Take on the Challenge of Complex Molecules

By: Cindy H. Dubin, Contributor

The global pharmaceutical analytical testing outsourcing market could reach $9.6 billion by 2025, with services to include cleaning validation, analytical standard characterization, and peak identification. Additionally, clinical bioanalytical testing will witness growth during this period, owing to the increasing number of clinical trials and increased regulatory guidelines aimed at improving drug discovery and development.[1]

Additionally, there is an increase in the number of deadly diseases such as cancer. This has created a need to increase the production of drugs and develop new drugs to reduce the burden on existing ones. These factors are also increasing the demand for high-quality analytical services[2], for example, the desire for analytical and bioanalytical methods that address the growing market for complex compounds and biologics. Added to this complexity is the quickened pace at which service providers are expected to help progress these products into the clinic. To this end, contractors are enhancing their knowledge base.

This annual *Drug Development & Delivery* report highlights some of the analytical testing services that leading contractors offer aimed at the increasing complexities of today's pharmaceutical pipelines.

Alcami: Playing a Role in Opioid Product Formulations

Alcami offers a range of services with extensive experience in development and validation utilizing various detection techniques. For peak identification specifically, mass spectrometry and NMR equipment, as well as standard characterization, are deployed. Moreover, Alcami has cleaning validation experience, particularly in its oral solid dose and sterile manufacturing facilities. Alcami also provides complete environmental monitoring and water analysis services. Alcami assists with API structural characterization, drug product formulation, and full-on method development/validation work in support of a product's lifecycle and production. At present, Alcami has more than 265 products in its portfolio. Alcami's API portfolio includes more than 90 clinical and 20-plus specialty commercial and generic products, and its drug portfolio encompasses more than 90 clinical and 65-plus specialty commercial and generic products.

Alcami's current contribution to the bioanalytical and biopharmaceutical space focuses primarily on antibody, protein, and peptide evaluations featuring cell-based bioassays, residual DNA analysis, particle identification, and extractable/leachable programs. "In the biotech area, we have invested in technologies and capabilities, including new qPCR equipment," says Director of Biotechnology for Alcami Vernon K. Dailey.

In the past year, one of Alcami's standout achievements, according to Jason T. Spacek, Director of Commerical Development for Laboratory Services, Alcami, was an analytical testing partnership that led to a client's successful submission of an opioid product. "As the opioid abuse epidemic worsens and becomes more prevalent in our communities, Alcami works to combat the crisis by employing an experienced abuse-deterrence team. This highly skilled unit ensures opioid products formulations can stand up to the harshest abuse conditions and regulatory scrutiny."

AMRI: Complex Compounds & Formulation Characterization for Large & Small Molecules

Extractable and leachable evaluations are becoming increasingly more vital to patient safety considerations and gaining regulatory approval. Heightened requirements necessitate manufacturers to seek subject matter experts who are aware of these industry trends and changes in the regulatory landscape for medical device evaluations and container qualification. Across its suite of discovery, development, and analytical and solid state capabilities, AMRI offers bioanalytical methods for the extraction and quantitation of drugs and metabolites in biological fluids and tissues including, but not limited to, biological sample preparation, rapid selection and method development, quantitative bioanalysis, radiometric detection, and structural characterization of metabolites by LC/MS/MS, LC/NMR, capillary NMR.

There is also growing interest toward biologics, controlled substances, and more chemically complex compounds. "It is AMRI's intent to ensure that the company's global analytical services have the expertise and technologies to serve this increasing demand from customers and meet the evolving requirements for healthcare professionals and patients," says Pamela A. Smith, PhD, Vice President of Analytical and Solid State Services, AMRI. "As the market for complex compounds and biologics continues to grow, there is a significant need for established analytical and bioanalytical methods that can help improve discovery and development."

Recently, AMRI introduced ultra-high resolution Q-TOF mass spectrometry services for large and small molecule analyses. Using state-of-the-art instrumentation enhances the company's capabilities in analysis and data interpretation for small and large molecules, including biologic drugs, metabolites, and polymers to meet the expectations outlined in the ICH Q6B Specifications.

In addition, AMRI offers a range of analytical technologies to characterize biologics and biosimilars, such as HPLC (RP, IEX, SEC, IC), gel electrophoresis (SDS-PAGE/Native PAGE; IEF) for separation and purity evaluation, N-Terminal Edman Sequencing and amino acid analysis for protein identification, MALDI-TOF mass spectrometry for molecular weight determination, dynamic light scattering, SEC MALS, and SEM for aggregation state evaluation, and a variety of spectroscopic techniques (NMR, UV/VIS, IR and Raman) for fingerprinting of macromolecules. In addition, ligand binding and activity assays together with LAL endotoxin testing are provided to support batch release of biologicals and biosimilars.

"Having advanced analytical technologies that provide important information from different dimensions is essential to probing the physical and chemical attributes of these increasingly complex systems, such as drug-conjugated antibodies," says Dr. Smith.

AMRI also sees growing interest for advanced formulation characterization approaches, patient-centered innovations, and emerging modalities for oncology. "This is particularly exciting for AMRI as we continue to strengthen our analytical and solid-state services, expertise, and technologies to support a variety of complex needs for our customers through our pre-formulation, material science, particle engineering, and analytical testing services," Dr. Smith says.

Aztech Sciences Inc.: Comprehensive Physical Analysis of Compounds

The analytical services arena has increased within the past few years in the area of specialized testing. When manufacturing of a drug product, analytical prudence is premium, leading to a need for a cleaning validation procedure and to be in full compliance with regulatory agencies.

"This will confirm that the production equipment is prepared to perform its duty for the required manufacturing method," says Alvin Persad, PhD, President/Co-founder, Aztech Sciences Inc.

Dr. Persad says that the cleaning validation method is analyzed by HPLC/GC, depending on the product's physicochemi-

Aztech's lab designed and prepared a formulation product, along with HPLC development.

cal properties. Specialized stainless steel (ss) plates give a representation for the surfaces of the production equipment. These plates will be the platform for the wet chemistry reconstitution analysis and sampling, followed by HPLC/GC. These results will provide the specification criteria to be set.

HPLC/GC, among others, can generate a partial Certificate of Analysis (CoA) from an API. Standard characterization and peak identification using analytical methods can be very lengthy, depending on the stage of early development and emphasis on the client's request. "As an example, our lab designed and prepared a formulation product, along with successful HPLC development, to confirm the analytical testing results within one week," says Dr. Persad. "The client was able to get these results to a preclinical testing site for animal dosing."

Catalent: Product Characterization Through Client Partnerships

Catalent Biologics has acquired state-of-the-art frontline analytical capabilities and equipment to offer comprehensive analytical testing services for biologics. These range from early-phase screening to later-phase product characterization, and encompass chemistry, biochemistry, and biological techniques.

"Analytical standard characterization and peak identification are set to show tremendous growth in the next few years," says Abhishek Mathur, Director, Biologics Analytical Services, Catalent. "We have invested heavily in supporting these services and in making sure we have the right capabilities to help characterize the standards thoroughly and pedantically."

Unique challenges have arisen with the rapid growth of biologics analytical demand, and ICH, USP, and FDA regulations are evolving to address new biologic entities. "The new biologics are more complex, and the pace to see them progress into the clinic is faster than ever previously seen," says Dr. Mathur. Concurrently, the biosimilar market requires the comprehensive analysis of molecules faster than ever before. Sponsors are competing to be the first to market with new original biologics or biosimilars.

The need to bring drugs to market faster, at minimal expense is driving the increased demand for high-quality GMP analytical services and outsourcing characterization work. The increase in biologics characterization to understand the product from the beginning of development is, in turn, driving the need for strategic partnerships. "The partnerships that Catalent is forming ensure that the understanding of the product is built over time, consistently and coherently," says Michael Merges, Director of Strategic Growth, Biologics, Catalent.

Mathur adds that characterization of drug functionality and efficacy beyond cell-based potency assays is being increasingly requested. As a result, Catalent is adopting rapid cell-based functional assays for early screening before the drug is put into humans. "The advent and rapid rise of quantitative mass spectrometry with supporting technologies and instrumentation in the last decade has been instrumental in pushing the limits of characterization further," says Mathur.

Catalent's experience suggests there is a rising need for drug sponsors to engage early in the process to learn about the product. Recently, Mathur's team worked with a large biotech drug manufacturer on a new and specialized program that was not typical for its conventional line of drugs and pipeline. The need was for successful engagement during pilot runs to ensure that the product had the desired quality attributes before full-scale production commenced. These requirements included method validation and rapid turnaround (~five days from sample availability to test results) for the analytical testing, which primarily required mass spectrometry characterization.

"With the drug candidate being a novel modality, additional challenges existed in terms of peak characterization and data processing," says Mathur. "The work required seamless and frequent communication between Catalent and our partner to maintain streamlined operations and stick to the tight timelines. Data processing took much longer than anticipated due to the novelty of the product, and our partner acknowledged the "extra fuel" that was required to drive the project to success. Frequent communication between the scientists at Catalent and at our partner's lab formed the key to the success of the project, which was realized to have strong flavors of 'a new scientific learning opportunity.' This is an excellent example of science excelling through a successful scientific collaboration."

Frontage Laboratories: Release, Stability, & Comparability Testing of Formulated Biologic Drugs

Analytical testing for biologics usually require an array of methods to elucidate the multifaceted aspects of structural, physicochemical, and functional properties. Frontage Laboratories has a range of capabilities to conduct testing release, stability, and comparability testing of the biologic products. To that end, Frontage scientists perform analysis of the critical

A Frontage scientist using the Maurice instrument.

quality attributes that need to be clearly assessed based on the potential impact on the manufacturing process, and clinical and regulatory requirements.

Large molecules, such as proteins, usually contain hierarchic levels of structures: primary, secondary, tertiary, and quaternary structures. Degradation of these structures can potentially impact the quality, potency, stability, and clinical outcome of the protein therapeutics, and can occur at all levels of the structure. The degradation pathways of a protein can often cause changes in charge, size, and mass. Frontage deploys several analytical methodologies, such as chromatography, electrophoresis, and mass spectrometry to detect these changes.

"Our analytical scientists can also develop protocols to monitor changes of charge variants or size (aggregates) species using chromatographic or capillary electrophoretic methods," says Min Zhao, PhD, Director, Analytical Services-Biologic Product, CMC Services, Frontage Laboratories. "The icIEF/CE-SDS methods based on our new Maurice system enable separation of charge/size variants in a stable pH gradient established by ampholytes in a capillary, and detected by whole column imaging with UV absorbance or native fluorescence."

Similarly, cIEF/CE-SDS methods can be established using the CESI 8000 Plus ESE-MS Instrument. Another method that is commonly used by Frontage scientists for analysis of charge variants is CZE method. The CZE separation, based on CESI 8000 Plus ESI-MS, has a significant advantage in that it can directly interface with the electrospray ionization (ESI) mass specrometer, Dr. Zhao explains. "The new CESI system offers an unprecedented analytical method to detect the charge variants by CE separation directly with a mass spectrometry."

With regard to the advent of novel therapeutic modalities for cancers, such as engineered CAR T-cell therapy and cancer gene therapy, there is increasing demand for developing new and unconventional methods for analyzing these therapeutic agents. Frontage Laboratories is at the forefront of these techniques, Dr. Zhao says. For example, CAR T-cells are produced using genetic modification of the blood cells harvested from patients. The CAR T-cells are tested for identity based on cytochrome oxidase or short-tandem repeat profiling and DNA fingerprinting, while the viral vectors are analyzed by sequencing of transgenes and restriction enzyme digestion.

"There is also a need for quick assays to assess the sterility and microbial growth so as to provide real-time release of the CAR T-cells," says Dr. Zhao. "In the next decade, it is expected that significant increase in demand for the unconventional and quick tests are required to support testing of safety, quality, and efficacy of the novel therapeutic modalities."

Metrics Contract Services: Analytical Chemistry for Complex & New Molecules

An increase in the number of deadly diseases has created a need to increase the production of drugs and develop new drugs, escalating the demand for high-quality analytical services. Metrics Contract Services is familiar with these therapeutic classes of drugs. "Our experiences have led us to understand that phases of development for such drugs can be much different than with medicines treating less-life-threatening conditions," says Keith Moore, Vice President, Analytical Services. "It's important to understand the regulatory pathway to ensures a balance of customer expectations. As an example, the path to approval for certain type of drugs can be much shorter and thus, the amount of data to support approval is much more limited than traditional drugs. Therefore, it is critical to leverage the limited amount of data to support their submission."

As an example, a customer selected Metrics Contract Services to support a Phase II program for a drug addressing a unique medical condition. Phase I activities

were completed by another CDMO, from which Metrics received the analytical methodologies and structural information of the active molecule. The previous CDMO utilized traditional RP-HPLC with UV detection set-up in developing an assay and impurities procedure.

"The structural properties of the molecule lead us to question the detection selection as well as the potential degradation pathways," says Mr. Moore. "After just a few experiments, Metrics chemists determined that the salt form of the drug was being detected on the UV instead of the drug itself. We instead used Charged Aerosol Detection to develop a new testing procedure and to analyze all previous Phase I supplies to provide accurate results of the chemical purity. We also utilized LC-MS to confirm our initial hypothesis. Scientific technical competency and due diligence allowed us to successfully set up the proper techniques for the client's Phase II program."

While pharmaceutical scientists continually develop different formulations and newer classes of molecules, the foundation of analytical chemistry already firmly established in support of formulation development can be readily modified. "For example, we are seeing more polymer-based drug technologies, multi-particulate formulations, and dual-active formulations," he says. "While these can be challenging to work with, analytical scientists know that component, material, and composition understanding is the key to finding the right approach to analysis. Whether it is related to the diluent/dissolution media solvent selection or appropriate extraction techniques, the foundational elements utilized within the analytical chemistry sector still can be applied to fully characterize the drug components."

UPM Pharmaceuticals is a full-service CDMO with a dedicated analytical development group.

UPM Pharmaceuticals: A Variety of Platforms to Analyze Complex Drug Substances

As the pharmaceutical industry continues to experience consolidation and downsizing, more aggressive outsourcing efforts are underway with regard to analytical services. UPM Pharmaceuticals is a CDMO that uses a Quality-by-Design (QbD) approach to method development to ensure that the most appropriate and robust techniques are developed for each specific application. This approach also ensures that analytical methods are developed from the start to transfer to commercial operations. UPM accomplishes this through the use of diverse array of technology platforms, including the latest UPLC/HPLC, GC and FTIR systems, particle size and TOC analyzers, UV spectrophotometers, and state-of-the-art software systems for data acquisition and document management.

"Not limiting itself to a specific platform makes UPM's analytical services group highly versatile and capable of responding to a range of needs, including

the development of methods for novel compounds and controlled substances," says Daniel Dixon, Vice President of Quality Control, UPM Pharmaceuticals.

Collaboration between UPM and its clients is an important facet of the approach to analytical method development. Similarly, close cooperation with other fully qualified laboratories that have complementary capabilities ensures that UPM can provide the entire spectrum of analytical support required for drug development and commercialization, says Mr. Dixon. In addition, UPM has worked with outside contractors to develop specific HPLC columns for the chemical entities it tests. "As a CDMO, it is paramount to have an analytical group that is agile and aware of the trends in order to handle these more complex methods as they come along," he says. "Specifically, we have increased our staffing and knowledge base to develop the more complex methods required for the complex drug substances in today's pharmaceutical pipeline." ◆

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GENE-EDITING TECHNOLOGY

How CRISPR-Cas9 Technology Will Play a Vital Role in the Future of Human Therapeutics & Drug Discovery

By: Kevin Holden, PhD

INTRODUCTION

The burgeoning gene editing market is already projected to reach $7.5 billion by 2024. Contributing to this growth are the intensified research and development (R&D) efforts by pharmaceutical and biotechnology companies, primarily due to the role that gene-editing technologies can play in the emerging area of personalized medicine. Indeed, a recent review suggested that known mutations in over 3,000 genes in the human genome can be linked to genetic disorders or a disease phenotype. Recently, the CRISPR-Cas9 technology (Clustered Regularly Interspaced Short Palindromic Repeats – and associated nuclease) has emerged as not only a potential therapeutic itself but also a powerful new research tool. Although initially identified in the mid-1990s to early 2000s as a form of bacterial immunity capable of editing genes, it wasn't until 2012 that several groups – notably the laboratories of Jennifer Doudna, Feng Zhang, and George Church – demonstrated that a version of this process could be utilized to edit any gene in any cell, including human cells. Since then, CRISPR-Cas9 gene editing has emerged as an essential tool within the research community, and it is changing the way scientists are able to conduct experiments. Let's explore how this technology can be utilized in research efforts toward the development of new therapies and how it will play a vital role in the future of biopharma and drug discovery.

FIGURE 1

THE CRISPR TOOLBOX

Although initial CRISPR experiments documented its use for performing simple DNA edits, applications now include the ability to delete genes, transiently inhibit (CRISPRi) or activate (CRISPRa) genes, insert entire genes, and edit regulatory regions with relative ease in a wide range of cell types. Furthermore, CRISPR can be utilized to screen entire gene families of genetic pathways, or to study gene regulation through the identification and analysis of promoter and enhancer regions in non-coding regions of the genome. The adaptability of CRISPR is leading to its widespread adoption within the research community. Following this trend, a recent industry survey conducted by Synthego, a genome engi-

neering solutions company, showed that 87% of new CRISPR users are also new to gene editing as a whole, indicating the tremendous interest in the process' simplicity and prevalence, as compared to other techniques.

GENE EDITING BEFORE CRISPR

Despite the high adoption rate of CRISPR gene editing for use in human therapeutics and drug discovery, there is still a percentage of scientists utilizing previously developed technologies for this purpose. For example, Meganucleases, Zinc Finger Nucleases (ZFNs), and transcription activator-like effector nucleases (TALENs) are all technologies developed for gene editing as alternatives to viral delivery systems for therapeutic in vivo editing of human cells. However, each of these alternatives to CRISPR depends on a more complex system for targeting and editing genes and are typically less efficient. In addition, they are not as malleable as CRISPR and so cannot be easily repurposed for other applications. Similarly, RNA silencing technology – also known as RNA interference – has long been used for drug discovery research to knockdown genes in cell lines in order to study drug targets or generate models for disease. However, this approach is far less efficient than using CRISPR: gene silencing using CRISPRi is more pervasive due to its less transient nature, and permanent gene knockouts are relatively simple to generate and can be stored for later use. CRISPR is not the only solution for conducting effective gene editing research; however, it does provide distinct advantages in terms of time, ease of use, and application flexibility that are important for scientists to consider for their research projects.

THE ROLE OF CRISPR IN HUMAN THERAPEUTICS

As an alternative to viral delivery systems and TALENs, CRISPR-Cas technology represents a potential gene therapy delivery system in its own right. Currently, many groups are focused on utilizing CRISPR to perform either in vivo editing of human cells – everything from the eye, to neurons and liver cells – or for performing ex vivo therapies. CRISPR could also potentially be used to undertake germline editing of cells and embryos for therapeutic use.

CRISPR-Cas9 genome editing in vivo refers to the delivery of CRISPR components directly to diseased cells in a living organism, such as a human being. Until recently, only viral vectors or TALENs could be utilized for this approach. Therapies relying on an in vivo editing approach have the advantage that they may be able to target and alter multiple cell types (or organs) at once. A recent report showed that delivery of CRISPR-Cas9 components directly into mouse liver cells in a model of human hereditary tyrosinemia disease could correct disease phenotypes – demonstrating that CRISPR-Cas9–mediated genome editing is feasible in adult animals and has the potential for correction of human genetic diseases. Due to the limited number of CRISPR-Cas9 delivery systems available, an early focus of in vivo editing, for example, has been to treat inheritable diseases of the eye by injecting CRISPR-Cas9 components directly into the eye. Recently, CRISPR medicine company Editas Medicine suggested their first foray into human CRISPR trials would take place this year, but in May 2017, they announced their timeline had been delayed. The proposed study, which will target a rare genetic eye disorder, is now expected by mid-2018.

Ex vivo therapies differ from in vivo therapies in that they involve the removal of a donor cell population, typically from the original host. These donor cells are then genome edited (eg, using CRISPR-Cas9) in a lab and then transplanted back into the patient. If the edited cells are to be transplanted into a different donor, the cells must be allogenic. This method of CRISPR-Cas9 cell therapy has an advantage over in vivo approaches as the CRISPR-Cas9 components can be delivered to the target cell population using a variety of approaches, including electroporation, lipid transfection, or with viral vectors. Because of this, very high editing rates can be achieved. In addition, the dosage to the patient can be controlled more easily than it can be with in vivo-based therapies.

In recent months, the first instance of human embryo editing occurred as well as the discovery of a modified version of CRISPR, which can be used to track RNA in live cells using RNA-targeting Cas9. This methodology could potentially allow doctors to repair molecular mistakes resulting in diseases such as myotonic dystrophy types 1 and 2, the most common form of hereditary amyotrophic lateral sclerosis (ALS) and Huntington's disease. These discoveries demonstrate the breadth of research currently being performed using CRISPR.

As CRISPR continues to make headlines as a potential cure-all for diseases from Huntington's disease to cancer, it is important to differentiate between what is possible with the gene-editing tool at present, and its future potential.

Current roadblocks surrounding CRISPR's immediate advancements in disease elimination include repeatability in experiments and approval in human clinical trials, which are still years away from becoming routine in the United States. The

first human trial involving CRISPR in the US was reviewed and given approval by the US National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC) in June 2016. However, this is not the final hurdle; the proposal from the University of Pennsylvania will still need to be approved by the US FDA before the study can move forward. Once full approvals are in place, the study will take an estimated 2 years to complete. Three trials involving CRISPR are currently being planned by researchers at Peking University in China; these will investigate CRISPR's efficacy against bladder, prostate, and renal-cell cancers. Each of these studies across both China and the US are in the very early stages, and most do not yet have approval, meaning that there is a long way to go before therapy involving CRISPR is commercialized and used within the clinic.

Despite these hurdles, companies focused on a CRISPR medicine approach, such as CRISPR Therapeutics, Intellia Therapeutics and Editas Medicine continue to develop the technology with a clear focus on the dynamic combination of pharmaceuticals and gene editing, propelling future advancements in the field. A new player, Casebia Therapeutics, was derived from a 2015 partnership between Bayer and CRISPR Therapeutics, combining their expertise to make headway in drug discovery. To form this initiative, proprietary gene-editing technology from CRISPR Therapeutics was combined with Bayer's knowledge rooted in protein engineering and disease-specific matters. This strategic partnership pioneered the move toward the development of targeted delivery systems and novel treatment options for diseases. Editas Medicine is another company combining pharmaceutical and gene-editing expertise to develop specific therapies based on CRISPR technology. In 2015, Editas entered a strategic collaboration with Juno Therapeutics, a biopharmaceutical company, to combine its CRISPR technology with Juno's experience in creating chimeric antigen receptor and high-affinity T-cell receptor therapeutics to develop cancer management and treatment options.

THE ROLE OF CRISPR IN DRUG DISCOVERY

Currently, CRISPR is still largely confined to the basic research stage of the drug discovery process. However, given its ease of use, CRISPR's potential spans each stage of the drug discovery process; from the identification and validation of new therapeutic targets, to investigations surrounding mechanisms of action, and the creation of screens to identify genes that regulate cell survival processes. Although there remains a great deal for the pharmaceutical industry to learn about contemporary gene editing, there are several applications that standout as areas for growth over the coming years.

Antiretroviral Therapy

Retroviruses are a group of single-stranded positive-sense RNA viruses with a DNA intermediate; retroviruses insert a DNA copy of their RNA genome into the host cell in order to replicate. Examples of retroviruses include HIV and human T-cell leukemia virus (HTLV). Research into retroviruses has made significant progress using CRISPR. For instance, in a 2016 study, a team of researchers were able to locate and remove the HIV genome from infected T cells with no adverse effects to the cells, which continued to grow and divide as normal. In addition, following the removal, the T-cells appeared to remain immune to new HIV infections in the future. Most viruses create proteins by transcribing DNA into RNA, while retroviruses utilize a different method. RNA is reverse-transcribed into DNA and is then integrated as a provirus into the genome of the host cell. Then, the provirus moves through the typical transcription and translational process, expressing the virus' genes. These retroviruses have many modern-day applications, such as cancer research and gene therapy.

Disease Model Organisms

The key to successful drug development is the availability of suitable model systems with which to make early drug development decisions. Traditional disease models include in vivo applications using rodents, and in vitro experiments using human cell lines. CRISPR has enabled mouse genomic core facilities around the world to exponentially speed up their development of transgenic mouse development. In some cases, transgenic mouse development for gene knockouts, knock-ins, or single nucleotide variants (SNVs) that once took 6 to 12 months can now be completed in less than half the time.

CRISPR can also advance the use of novel animal models for drug development research. Creating a new disease model can be a laborious process demanding considerable financial investment – and even then, the task is often limited to a few species that come equipped with a good tool kit for genetic manipulation. One such novel model organism is the ferret. CRISPR has enabled researchers to engineer the genome of ferrets in order to modify their susceptibility to flu infections, a critical

change since unlike rodent models, ferrets sneeze when infected – a much more human-like response. Moreover, CRISPR also allows traditional model organisms, such as Zebrafish and C.elegans, to be engineered in a much shorter timescale than previously possible. The use of these organisms as models for understanding human cell biology, development, and neurobiology may negate the need for more time-intensive and costly mammal models in the future.

Another benefit to utilizing CRISPR to develop disease models is its ability to be used for multiplex gene editing. For example, CRISPR can be utilized to make multiple genetic changes at once, which more closely approximates human pathology. Many diseases are multigenic as opposed to monogenic, and these new models can contribute substantially to ensuring drug evaluation is more accurate and translational.

Cell Line Development

In addition to the generation of whole animal models for disease research and drug discovery, the generation of knockout or knock-in cell lines can also be a critical tool in the process. For example, the generation of cancer cell lines for modeling different cancer genotypes are useful for screening potential and existing drugs for sensitivity. Alternatively, individual gene deletions, SNVs, or combinations of these can be generated using CRISPR in established cell lines in order to generate disease genotypes or phenotypes for use in drug discovery. Furthermore, CRISPR-Cas9 gene editing can be applied to embryonic stem cells in order to produce disease genotypes and subsequent phenotypes when programmed to develop into desired cell types or organoids. Through this approach, functional organ tissues can be modelled in vitro and tested for sensitivity and reactivity to drug candidates.

FUTURE CRISPR-BASED THERAPIES & CONSIDERATIONS

Taking into consideration the cases and applications of CRISPR we have already discussed, it is clear that future progress and impact with regard to drug discovery will center on chimeric antigen receptor (CAR) T-cells, or receptors that have been engineered onto a T-cell, and stem cell research. With a technique known as adoptive cell transfer, CAR cells are currently being tested as a potential cancer therapy. Researchers remove and modify T-cells, manipulating them to express receptors specific to the form of cancer a patient possesses. From there, the T-cells are reintroduced back into the patient, where they can "seek" and destroy cancer cells.

Research surrounding cancer therapy using T-cells continues to become more prevalent. In July 2017, the Independent Citizens Oversight Committee (ICOC) of the California Institute for Regenerative Medicine approved a $5.8- million award to researchers at the University of California San Diego School of Medicine to develop a new immunotherapy in which patients' cells would be equipped with a special receptor to recognize and target cancer stem cells, whose survival abilities often render standard therapies ineffective or short-term.

CRISPR has made substantial strides in furthering research and drug discovery within the past few years, and the role of pharmaceutical companies throughout the process will continue to grow as these breakthroughs are made. One important thing for researchers in the areas of pharmaceuticals and drug discovery to remember is that CRISPR is not a one-size-fits-all technology. It is important for scientists to examine each desired goal and projected outcome to fully understand the most effective methods for conducting gene editing. We have a lot to learn as we step into the intersection where CRISPR and pharma converge, but the technology's pervasive and efficient nature has us on the right track for a successful future in the world of drug discovery. ◆

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BIOGRAPHY

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ANTIBODY THERAPEUTICS

Teneobio's Next Generation of Multispecific Antibody Therapeutics

By: Omid Vafa, PhD, MBA

INTRODUCTION

Teneobio has developed unique technologies, including a transgenic rat platform, UniRat®, expressing human heavy chain antibodies (UniAbs™) and a state-of-the-art sequence-based discovery engine to create novel multispecific antibodies for various therapeutic indications. In addition to therapeutic antibodies, UniAb binding domains can be successfully used as 1) antigen recognition domains on CAR T-cells, 2) targeting moieties for nanoparticles, 3) antibody drug-, toxin- or radiolabel-conjugates, and 4) viral payloads (eg, to modify the tumor microenvironment). Using this unique technology, Teneobio has identified an unprecedented number of novel anti-CD3s, which in the context of bi- or multispecifics, enable maximal T-cell redirection for tumor cytotoxicity and minimal cytokine release. Teneobio's unique capabilities and anti-CD3 platform are being applied to develop a number of breakthrough multispecific therapeutic candidates to treat hematological and solid tumor cancers. Its lead mutispecific therapeutic program, anti-BCMAxCD3, is in preclinical development for a planned IND submission in 2018.

ANTIBODY DISCOVERY

The past 30 years has seen a rapid evolution of therapeutic antibody technologies. A transformative milestone was the generation of transgenic human Ig rodent platforms, which enable the discovery of fully human antibodies with considerably less immunogenicity, overcoming the need to chimerize, humanize, and affinity mature mouse antibodies.[1] A survey of more than 50 currently marketed antibody therapeutics further highlights the fidelity and success of rodent-derived antibodies compared to *in vitro* display approaches to antibody discovery.[2] Not surprisingly, *in vivo*-derived antibodies have advantages conferred by physiological selection for critical quality attributes, including stability, solubility, and high affinity. In contrast, *in vitro* display methods lack these advantages. Hence, transgenic human Ig rodents have become a mainstay of therapeutic antibody discovery in the biopharmaceutical industry.

In the 90s, the engineering of antibodies extended beyond humanization and affinity maturation technologies to include the rational design of antibody Fcs through the selection of isotypes, the engineering for enhanced or silenced immune effector functions and the design for extended or reduced half-life.[3] The generation and engineering of antibodies (eg, scFvs, llama VHHs, human VHs) or alternative scaffolds (eg, DARPins, Centyrins, Fynomers) further afforded the ability to generate bi- and multispecific therapeutic candidates through the assembly of modular domains that were linked chemically or by amino acids.[4-6] Additional technologies involved the "knobs-into-holes" Fc heterodimerization and variations thereof, to enable bispecific generation in the natural and structurally conserved antibody format.[6] Through the years, an explosion of multispecific formats ensued, some of which progressed to clinical trials while others failed in development from challenges in manufacturability or limiting biology. With this backdrop, the next generation of transformational antibody therapeutics will reach beyond the monospecific, bivalent format toward physiologically compatible and developable human multispecific antibodies with improved or *de novo* biology, overcoming the therapeutic limitations of native human IgGs.

"The advents of immune-oncology checkpoint inhibitors and multispecific antibody technologies enable the redirection of the immune system for targeted killing of cancers of interest. The past decade has seen an exponential increase in such therapeutics, including CAR T-cell therapy, directed nanoparticles delivering payloads, antibody drug-, toxin-, and radiolabel-conjugates, etc. Teneobio's UniRat and TeneoSeek platforms, combined with a tool kit of engineering capabilities afford the opportunity to rapidly and effectively identify antibody therapeutic leads as well as UniDabs for a variety of multispecifics and novel cellular and delivery technologies."

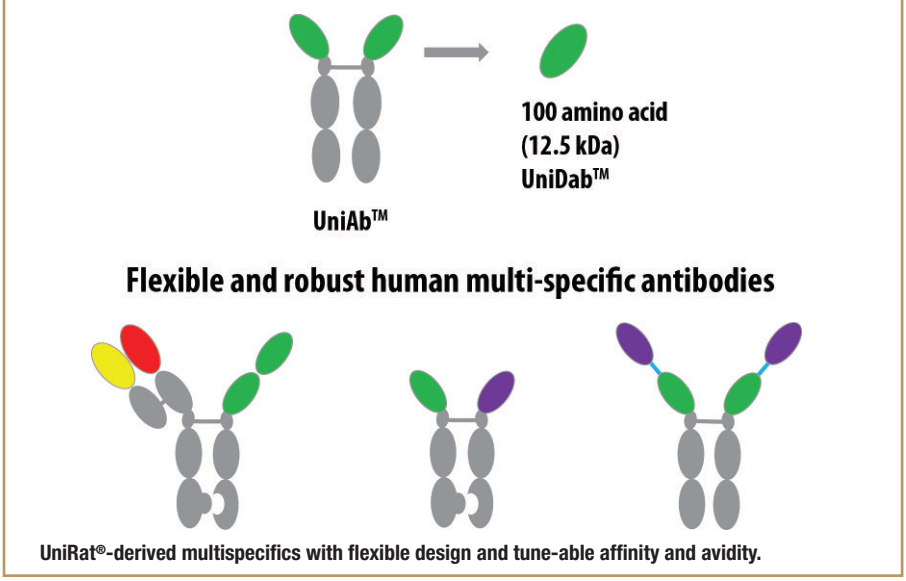
Advances in molecular and high-throughput technologies are enabling innovative approaches to discovering and capturing antibody diversity, previously limited by clonal loss in traditional hybridoma generation. Specifically, next-generation sequencing has enabled comprehensive profiling of full antibody repertoires of immunized organisms. Furthermore, using advanced methods of gene assembly, one can synthesize thousands of unique antibody sequences to be expressed and screened in high-throughput format. Taken together, these technologies enable rapid screening and identification of affinity-matured functional antibody leads at unprecedented speeds. Using naturally derived human antibodies from transgenic rats and state-of-the-art sequence-based antibody discovery, Teneobio is developing the next generation of novel and manufacturable multispecific antibodies as therapeutics for oncology, immunology, and infectious diseases.

DISCOVERY PLATFORMS: UNIRAT & TENEOSEEK

Teneobio's human Ig transgenic platform, the UniRat, is based on a triple knockout rat wherein the expressions of the native variable coding sequences and the heavy and light chain constant regions have been inactivated. The UniRat has been genetically modified to exclusively express the full human VDJ repertoire (all VH families), with transgenes of human heavy chain variable domains linked to a conserved rat Fc. Immunization of the UniRat elicits a normal antibody response that results in the expression of UniAbs, human heavy-chain-only antibodies of approximately 80 kDa, contrasting with the standard ~150-kDa human IgG. Importantly, heavy chain variable domains from the UniRat, UniDabs™, are the smallest antigen-binding units of a human IgG at approximately 12.5 kDa (~100 amino acids) and can be assembled as modular domains of multispecifics. Figure 1 illustrates a subset of such multispecific formats, enabling the generation of a plenitude of specificities against different epitopes on the same antigen or different specificities for different antigens. Heterodimerization of such heavy-chain-only multispecifics or their combination with standard heavy-light-chain formats is feasible, given that UniDabs (VH domains) do not interact with either kappa or lambda light chains *in vitro* or when co-expressed in cell lines.

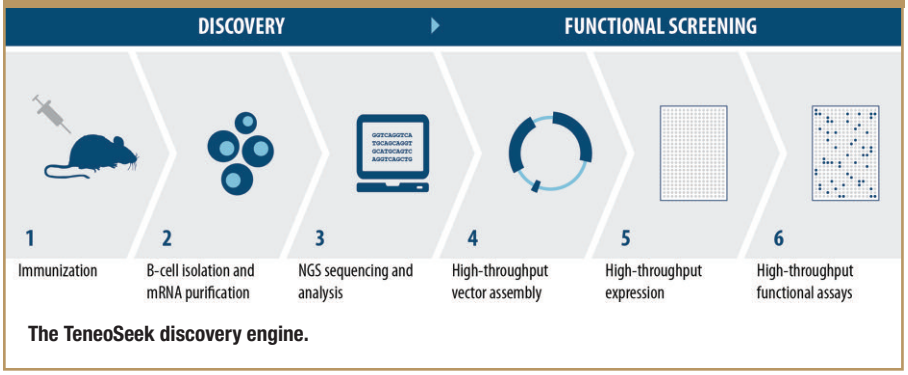
Complementing Teneobio's UniRat platform is a proprietary next-generation sequence-based discovery engine called TeneoSeek. The TeneoSeek discovery en-

FIGURE 1



UniRat®-derived multispecifics with flexible design and tune-able affinity and avidity.

FIGURE 2



The TeneoSeek discovery engine.

gine comprises three key components: 1) next-generation sequencing of the full repertoire of the immunized UniRat, 2) bioinformatic B-cell lineage analysis of human variable domain sequences to identify antigen-specific CDR families, and 3) high throughput gene assembly, expression and functional screens to identify leads of interest. Inherent in the bioinformatic analysis are the proprietary algorithms that eliminate variable domain sequences of CDRs containing post-translational liabilities (eg, cysteines, methionines, deamidation motifs, glycosylation residues, etc) as well as problematic surface patch residues that can contribute to instability and aggregation. The start-to-finish timeline, from immunization to lead identification of UniAbs, is approximately 4 months, one of the fastest in the industry (Figure 2).

The rich diversity of antibody leads obtained from UniRat immunizations, coupled with bioinformatic analysis of sequences and lineage afford the ability to identify specific UniAb members (from VH CDR3 families) against a broad number of epitopes and a wide range of affinities spanning pM to μM. Uniquely, UniDabs have been shown to access protein grooves and crevices on target antigens that are otherwise non-accessible with standard H2L2 antibodies, given the near double size of their paratopes. Modular UniDabs can then be rapidly assembled and further engineered for desired multispecificity and effector functions on human Fc backbones of interest. Of note, the highly manufacturable and stable UniDabs and their derived multispecifics, which have a melting temperature of ~60°C to 64°C, can be expressed at grams per liter and are easily manufactured in CHO cell lines. CHO cell supernatant yields of heterodimeric UniAb multispecifics are > 85% and can be purified using a single capture step process to 98% purity. The developability and expression profiles of UniAbs and their multispecific antibody derivatives are quite similar to that of standard antibodies and compatible with industry standard manufacturing platforms.

UNIQUE T-CELL REDIRECTION PLATFORM FOR CANCER THERAPY

Throughout the past decade, T-cell redirection using bispecific antibodies has provided favorable clinical outcomes in treatments of liquid tumors, including leukemia and lymphoma. Teneobio has used its technologies to provide unique solutions for T-cell redirecting therapies. The basis for the approach relies on the coupling of an anti-CD3 recognition domain with a targeting moiety as a fusion construct. In the past, a limitation to this approach has been partly target-related, given the difficulty of generating anti-CD3 antibodies, as well as CD3 biology. Specifically, limitations associated with the immunogenicity of CD3 epitopes and the industry's modification and/or humanization of less than a handful of known anti-CD3 antibodies (eg, OKT3 and SP34) have limited the application of this powerful approach to cancer therapy.[7] To address these limitations, the TeneoSeek discovery platform was applied to identify > 100 unique anti-CD3 sequences spanning different target epitopes and covering a broad spectrum of affinities from low nM to μM affinities. Largely enabled by sequence and repertoire lineage analysis, leads from these efforts have yielded a diverse collection of novel anti-CD3 antibodies with unique and differentiated biology.

Recent clinical utility and the therapeutic application of bispecific anti-CD3 antibodies have been complicated by adverse events, including cytokine release syndrome and neurotoxicity. In contrast to these first-generation anti-CD3 molecules, Teneobio's unique anti-CD3 platform is based on the access to a diverse set of anti-CD3s with different binding and T-cell activation profiles, decoupling tumor-specific cytotoxicity from cytokine release. A comprehensive analysis of a subset of these leads has yielded variants that can differentially kill cancer cells with minimal proinflammatory cytokine release, potentially increasing the therapeutic window. This would be particularly advantageous for anti-CD3 bispecifics with longer *in vivo* half-lives. The ability to tailor anti-CD3-based bispecifics for targets of interest offers prospects of a next generation of safer and improved therapies using clinically validated cancer cell targets. These safety

profiles are currently being assessed *in vivo*, and studies to date indicate that multispecifics derived from the UniAb platform exhibit mouse and monkey half-lives that are consistent with that of standard antibodies. Additional *in vivo* studies have validated the anti-CD3 platform, demonstrating the efficacy of the bispecifics in weekly dosing of mouse models. With a planned IND filing for 2018, the clinical validation of Teneobio's anti-CD3 platform and lead therapeutic candidate, anti-BCMAxCD3 (bivalent for BCMA, monovalent for CD3) for the treatment of multiple myeloma, may open new opportunities to address challenges related to efficacy and adverse events associated with T-cell targeting of liquid and solid tumors. To this end, Teneobio is applying its T-cell redirection platform in additional therapeutic discovery programs, including anti-CD22xCD3 and anti-CD19xCD22xCD3 for lymphoma and ALL as well as anti-PSMAxPSCAxCD3 for prostate cancer.

NEXT-GENERATION MULTISPECIFIC UNIAB-BASED THERAPEUTICS

The advents of immune-oncology checkpoint inhibitors and multispecific antibody technologies enable the redirection of the immune system for targeted killing of cancers of interest. The past decade has seen an exponential increase in such therapeutics, including CAR T-cell therapy, directed nanoparticles delivering payloads, antibody drug-, toxin-, and radiolabel-conjugates, etc. Teneobio's UniRat and TeneoSeek platforms, combined with a tool kit of engineering capabilities afford the opportunity to rapidly and effectively identify antibody therapeutic leads as well as UniDabs for a variety of multispecifics and novel cellular and delivery technologies. The ease of assembling multispecifics with modular binding domains enables the exploration of synergies to activate and redirect the immune system to cancer cells. Multispecific UniAbs and UniDabs can be assembled for improved affinity through increased avidity against targets of interest (eg, a bivalent heavy chain only anti-BCMA can competitively block APRIL ligand binding to BCMA). Additionally, UniAbs can be optimized for tissue specificity and selectivity through avidity for different antigens co-expressed on tissue targets of interest. Bi- or multiparatopic multispecifics can elicit gain-of-function or *de novo* activities, otherwise absent in monospecific antibodies or with their combinations. Biological activation or redirection of T-cells can be further explored to assess multispecific combinations that offer the best efficacy and safety profiles. Moreover, the application of UniDabs as extracellular domains for CAR T-cells has been validated and shown to be superior to the use of scFvs in some settings. The applications of UniDabs as antibody-drug/radiolabel conjugates, targeting moieties on nanoparticles, viral payloads to modify the tumor microenvironment, or imaging tools (given their relatively small size and tumor penetrance) offer endless possibilities to exploit these human variable domains for therapeutic benefit. Teneobio's unique platforms and antibody drug discovery capabilities are poised to deliver on these goals for a variety of indications, including oncology, immune disorders, and infectious diseases. ◆

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PACKAGING

Child-Resistant Features for Container Closure Systems

By: Stefan Hellbardt, PhD, Guenter Nadler, and Degenhard Marx, PhD

INTRODUCTION

Unintentional poisoning from drugs and other household chemical substances pose a hazard to children, in particular to those younger than 5 years of age. Curiosity and the desire to put everything into their mouths are placing young children at considerably higher risk for poison exposure compared to adults. Children will eat or drink anything regardless how it tastes. They like things that smell good, and are attracted by colorful packaging or content of products found at home.[1,2]

To address this issue in the US, Congress passed in 1970 the Poison Prevention Packaging Act (PPPA). Under the PPPA, the US Consumer Product Safety Commission (CPSC) has issued regulations that require child-resistant (CR) packaging for about 30 categories of hazardous household products and medicines. Child fatality numbers have declined substantially since the PPPA became law; from 216 cases in 1972 down to an average of about 33 per year from 2008 to 2013.[3] In addition, countries in Europe as well as Australia have successfully implemented similar regulations to protect children from poisoning. Others are on their way to introducing such requirements.

In 2012, the US CPSC responded to cases of accidental ingestion of medications by children resulting in serious health risks by issuing a rule requiring child-resistant packaging for any over-the-counter or prescription product containing the equivalent of 0.08 milligrams or more of an imidazoline [16 CFR Part 1700.14 (33)]. This class of drugs is widely used as an active ingredient for eye drops used to relieve eye redness and burning, as well as a decongestant for cough and cold medications. For the year 2012, the commission estimated that approximately 45 million units of ophthalmic decongestants containing imidazolines and 39 million units of nasal products were sold in the US. For ophthalmic products, some standard child-resistant, senior-friendly (CR/SF) packaging was readily available, in contrast to nasal administration devices, where no such devices were present. For nasal products, metering spray pumps are state-of-the-art technology. Although the metering function of the pump will restrict the access to the complete bottle content, this feature is not considered to be inherently child resistant. Consequently, the CPSC stated that nasal spray pumps, even when crimped onto the bottle, are not considered CR and that either the pump action or the over

FIGURE 1

cap needs to be child resistant.

In a review of causes of intoxication in children, 86% of emergency room visits for medicine poisoning were found to result from the child having access to an adult medicine. In 38% of cases, the medication was used by a grandparent, in 31 % by the mother, and in 12% by a sibling.[4] These findings led to the conclusion that the right balance between CR and SF is critical for drug packaging. Thus, it is important to provide a safe and reliable CR feature without affecting the use by patients, including elderly people (SF). An adult or senior user needs to easily understand the CR feature. Opening, usage, and closure should be possible given age-related limitations (eg, reduced dexterity). The CR mechanism needs to work on a sealed package that has not been tampered with, with the protective cap correctly re-attached after each use.

In addition, the requirements for nasal spray products as set by the FDA need to be respected. The CR feature should neither have an impact on spray performance or delivered dose, nor lead to stability problems due to incompatibility. Avoiding unnecessary costs in the pharmaceutical manufacturer supply chain is also important. Packaging components with a CR feature need to be easily managed on established filling and packaging lines.

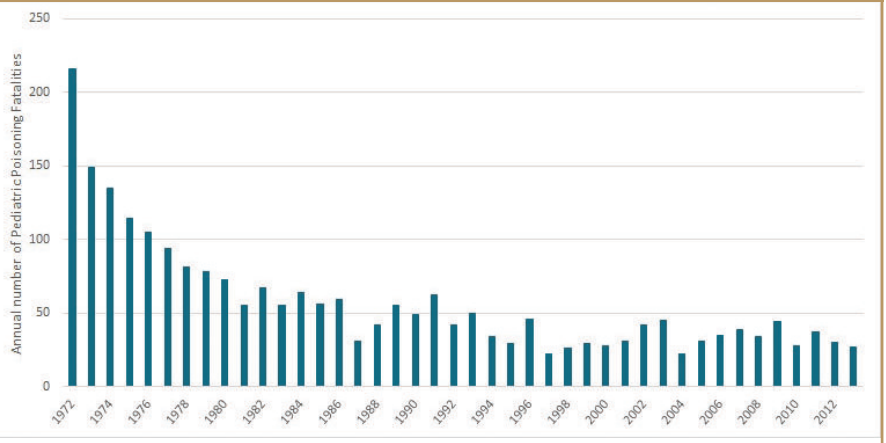
CR/SF PACKAGING FOR NASAL SPRAYS CONTAINING IMIDAZOLINES

As previously mentioned, the CPSC published in January 2012 a Notice of Proposed Rulemaking (NPR) to initiate a process for making products child resistant for formulations containing more than 0.08 mg imidazolines per package. This new rule requested that production stop of conventional, non-CR imidazolines-containing products by no later than December 2014. A subsequent decision by the CPSC extended this deadline to June 10, 2015. When the NPR became public, Aptar Pharma's experts recognized the relevance of this initiative and its impact on the market for nasal decongestants. Triggered by the aggressive timelines, activities were immediately started to provide a reliable solution for those pharmaceutical companies in need. Aptar Pharma approached its customers affected and started developing its first CR/SF nasal spray pump. When the final rule was published in December 2012, Aptar Pharma had already finalized a number of design studies on potential packaging solutions. To get such a product accepted by regulators and consumers, the requirements for CR as well as for SF must be balanced. All suggested concepts were built on the market-leading pump family, Aptar Pharma's Classic Line, representing the industry standard for nasal decongestant packaging in the US. Comprehensive consumer testing with all CR pump concepts generated valuable input from end-users. Prepared this way, Aptar Pharma was in the position to present a final design, and pilot molded samples only 8 months after the PPPA change was communicated.

For CR/SF certification, the complete assembled container closure system (CCS) consisting of the dedicated container (Aptar Pharma does not manufacture bottles) and the closure with the delivery device (ie, nasal spray pump developed and manufactured by Aptar Pharma) must be tested. Therefore, Aptar Pharma selected a range of market-relevant containers for its test series (ie, 15 to 30 ml). Fully assembled delivery systems successfully passed testing with children and seniors that were run by an external certified lab according to applicable guidance. Aptar Pharma's final systems successfully passed a CR test according US 16 CFR § 1700.20 and ISO 8317, with 50 infants aged 42 to 51 months, and an SF test with 100 seniors aged 50 to 70 years.

These results triggered a full industrial scale-up of molding capacity and the assembly units necessary to satisfy the forecasted demands. By end of 2014, Aptar Pharma and its partnering customers were united in a groundbreaking success story. All decongestant products using the new

FIGURE 2



Pediatric poisoning fatalities from 1972 through 2013 demonstrate an effective implementation of preventive measures. Graph is based on data from the U.S. Consumer Product Safety Commission, published May 2016.

"Drug development is a complex process with numerous potential stumbling blocks ahead. The primary focus is always on a medication's efficacy and safety. Innovative packaging solutions or dispensing systems, which enhance patient compliance, can certainly contribute to treatment success. In a growing older population with impaired visual faculty or dexterity, packaging solutions that can easily be handled by seniors are worth being considered."

Aptar Pharma "Classic Line" nasal spray packaging successfully passed the mandated CR/SF studies. By 2015, Aptar Pharma had already delivered a significant number of CR/SF nasal spray pumps units into the North American decongestant market. Numbers have been steadily increasing since then. Taking the next step, in May 2017, Aptar Pharma transferred manufacturing of the CR/SF nasal spray pump to the US, fulfilling its commitment to bring manufacturing capacity closer to its target markets. On the market for more than 2 years, Aptar Pharma's technical solution is backed by positive feedback from pharma companies that report convenient use by their respective brands.

Aptar Pharma's validated industrial capacity supported the switch for the existing market. By introducing an innovative CR/SF solution and proactively managing the change process, Aptar Pharma was able to turn the new guidelines into consumer-friendly and safe packaging.

SQUEEZE & TURN – A SOLUTION FOR SUCCESS

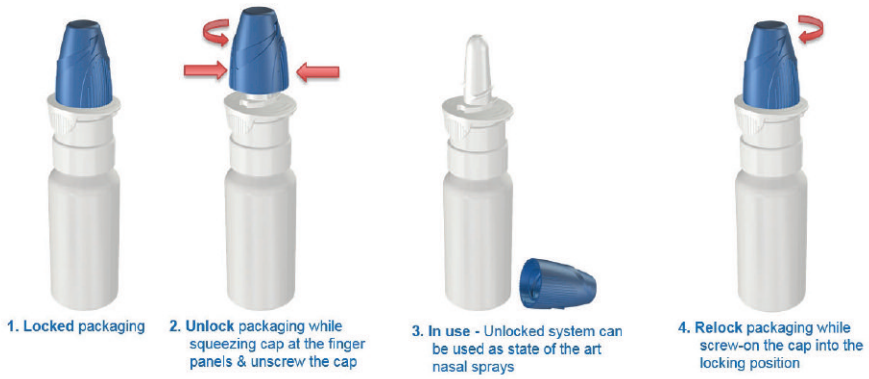
The principle behind the Aptar Pharma CR closure technology chosen is widely established in the consumer goods packaging industry. Thus, it is well known to users. Due to its intuitive functionality, it grants convenient access by adults. In contrast, the CR mechanism has been shown to reliably prevent against unintended access by children.

While customization is always an option at Aptar Pharma, a standard version is available, leveraging the market-leading pump family, Classic Line. Aptar Pharma is able to provide CR/SF testing certification from recognized institutions for this product line in combination with a wide range of HDPE bottles.

DERMATOLOGY TREATMENTS – NEED FOR NEW PACKAGING

As previously described, the requirements for CR packaging and exemptions are listed in the 16 CFR 1700.14 and therefore CR/SF tube closures for dermal drugs are widely available. New packaging solutions focus on supporting patient compliance. Treatment efficacy in chronic conditions like rosacea is critically dependent on the patient adhering to prescribed dosing schedules. As treatment can be required for a very long time, anything that supports patient's correct use of medication

FIGURE 3



Aptar Pharma Classic line nasal spray pump with CR/SF squeeze and turn cap is easy to use.

is key to successful disease management. Primary packaging can help increase convenient use of medications. Tubes, bottles, and jars are widely used, but recent evaluation supports the view that patients prefer pump dispensers to non-dosed systems.[5] By providing a consistent amount of product with each stroke, pump dispensers can improve treatment adherence, and reduce the risk of incorrect dosing.

In the last years, Airless Dispensing Systems have become more common in the pharmaceutical industry. Airless technology eliminates the need for air flowing back into the system to replace the dispensed product. For viscous bulks, which make up the majority in topical skin treatment, quick priming, reliable dosing, and effortless emptying of the package is ensured. Moreover, Airless Dispensing Systems are able to deliver their content at any dispensing direction. Wherever the target area on the body, all-angle dispensing will greatly support convenient use by patients. Finally, an appealing appearance, familiar from cosmetic and skin care products, reduces a potentially stigmatizing aspect of medication intake.

Just recently, the first rosacea treatment for facial redness was launched using the selective alpha1-adrenergic receptor agonist brimonidine as the active ingredient.[6] According to the guidance previously described, this drug needs to be packed CR. Consequently, the tube packaging at launch was equipped with a CR/SF closure. Following demand for more convenient and safe dispensing, experts at MEGA Airless, now a part of Aptar Pharma, entered into the development of a CR/SF pump dispenser for semi-solid formulations. It made perfect sense to combine airless dispensing solutions that were successfully positioned in the market, with commonly known principles of CR protection. The resulting Mini+cr dispenser is the world's first CF/SR airless dispenser for semi-solid drug formulations.

FIGURE 4

Aptar Pharma Mini+cr airless pump dispenser for semi-solid formulations.

The Mini+cr combines all benefits of airless technology. The pump dispenser enables convenient and clean dispensing with every stroke. All-angle use and emptying without extra effort are differentiating features of airless dispensing systems. Through the unique mix&match system, multiple combinations of dispensing heads and containers are possible without affecting the CR/SF feature. The Mini+cr pump is available in doses of 0.5, 0.8, and 1.0 ml per stroke. Bottom-fill technology allows flexible filling deviating from the maximum container volume of 30 ml or 50 ml. Airless dispensing technology ensures convenient, clean, and reliable access to the drug product. The CR/SF push-and-turn closure technology combines an intuitive opening mechanism for adult and senior users, with market-proven access restriction for infants. For certification, the Mini+cr passed a CR/SF test according US 16 CFR§ 1700.20 and ISO 8317, including the required number of infants and seniors. With Galderma[6] adding a pump system to its portfolio of rosacea treatments, the Mini+cr was successfully launched onto a regulated pharmaceutical market.

This solution is ready to be used with established (eg, testosterone-containing

meds) as well as new products (eg, ivermectine) which may pose a risk for children.

SUMMARY

Drug development is a complex process with numerous potential stumbling blocks ahead. The primary focus is always on a medication's efficacy and safety. Innovative packaging solutions or dispensing systems, which enhance patient compliance, can certainly contribute to treatment success. In a growing older population with impaired visual faculty or dexterity, packaging solutions that can easily be handled by seniors are worth being considered. To add to the complexity, many guidelines are in place, setting performance requirements for packaging material and delivery devices (eg, dosing consistency for spray pumps). Authorities will require solid data to confirm compliance with these rules. To further add to the list, one should not forget about governmental regulations that require special packaging for drugs with certain active ingredients, which have been discussed in the current article. Packaging suppliers familiar with applicable regulations and close enough to the target market can pave the way for complex developments by providing tailored solutions. Aptar Pharma has demonstrated its expertise by successfully introducing its first CR/SF nasal spray pump and the first dermal dispenser on the US market. Aptar Pharma will continue to be a strong and competent partner for drug developments in which the container closure system is more than a simple blister, tube, or bottle.◆

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Dr. Stefan Hellbardt is Vice President Business Development at Aptar Pharma. As a trained biologist, he earned his PhD at the German Cancer Research Center, Heidelberg. Holding various positions in the pharmaceutical industry, he gained more than 15 years of experience in clinical development. He joined Aptar Pharma in 2011 to lead the global business development of the newly created application field Dermal Drug Delivery. In his role, he is instrumental in delivering the expertise and service of Aptar to customers producing pharmaceutical products for topical dermal and transdermal application.

Günter Nadler is Director Business Development at Aptar Pharma. He graduated in Business Administration and in Mechanical Engineering and started his career at Aptar 17 years ago in R&D. Before joining the Business Development Team in 2010, he worked in different technical and commercial positions at Aptar Pharma and gained a wide range of knowledge within the pharmaceutical drug delivery industry. Lastly, he was Head of the Product Management Team for several years.

Dr. Degenhard Marx, following the study of veterinary medicine and the successful completion of his thesis at the University of Leipzig, joined the Arzneimittelwerke Dresden/Asta Medica co-operate research in 1992. In 2001, he took over a senior research position at Altana Pharma/Nycomed in Constance, Germany. During this time in the pharmaceutical industry, he collected ample experiences in the drug development of anti-inflammatory and cardiovascular drugs. In 2008, he became business development manager at Ing. E. Pfeiffer, Pharma Division, which became Aptar Pharma in 2010. Now he is Director Scientific Affairs at Aptar Pharma.

DEVICE REGULATIONS

Early Preparation Will Pay Big Dividends as EU Enacts New EU Device Regulations

By: Joanne Emmett

INTRODUCTION

In the medical device industry, it's long been evident that European regulations dating to the mid-90s have not kept pace with progress in developing new products. Current directives, for example, require only a critical evaluation of published literature for approval of new products that are functionally similar to existing ones. Now, those directives are giving way to new regulations that require Class III and implantable devices to undergo clinical investigation to show that they are equal or superior to other products on the market.

The new regulations also expand the list of devices that fall under the Class III designation to include spinal implants, devices that monitor and control active implants, nanomaterials, apheresis machines, and combination products. The industry must now prepare for what will surely be significant impact.

Spurring these changes: a pair of high-profile product failures that resulted in widely publicized recalls, both occurring in 2010:

- A French manufacturer of breast implants substituted cheaper industrial-grade silicone for medical-grade material, subjecting hundreds of thousands of patients to a 500% greater risk of leakage or rupture.

- A US maker of orthopedic products said its metal-on-metal artificial hip joints would last about 15 years, but the devices experienced a high rate of very early failures. Patients endured extreme pain and complicated, costly replacement surgery, and more than 11,000 lawsuits are still pending.

These events underscore the reality that failure is a sometimes necessary companion of innovation, and product flaws — whether they occur in automobiles, consumer electronics, or medical devices — are part of the process. Stringent and thoughtful regulation is vital to protecting patients as technology evolves, ensuring that new products meet or, ideally, exceed the standard of care.

HERE'S WHAT'S CHANGING

Following nearly 4 years of debate, the European Commission in mid-2016 approved plans to replace EU directives on active implantable medical devices (90/385/EEC) and on medical devices (93/42/EEC) with a single medical device regulation, and to replace a directive on in vitro diagnostic devices (98/79/EC) with a regulation on the same subject. The changes, which explicitly establish manufacturers' responsibilities for device quality, performance, and safety, affect a wide range of products — from contact lenses and pregnancy tests to X-ray machines, hip implants, pacemakers, and HIV blood tests.

The changes affecting in vitro diagnostics are particularly significant, constituting a major overhaul of the rules that will require secondary legislation and best practice guidance that have yet to be enacted.

The rationale is to provide more robust evidence of product efficacy and patient safety prior to market approval. Because the implications are complex and far-reaching, both new regulations have extended phase-in periods — 3 years for the medical device rules and 5 years for in vitro diagnostics. These lengthy transitions

are intended to give the device industry ample time to prepare for these and other significant changes.

Attention on Pathway Toward CE Mark

The transition to the new medical device and in vitro device regulations will require diligence on all existing CE marked certificates between 2020 and 2025, the effective date varying based on the product. That means all products will require recertification according to the new rules over a period of about 4 to 6 years.

Notified Body Recertification

Notified Bodies (NBs), organizations accredited by EU member states to assess products for market approval, must be recertified and redesignated under the new regulations. NBs also will face more stringent oversight by national authorities. The number of these entities has already been falling due to stricter accreditation requirements, leaving only about 60 overburdened NBs in existence today — and that number is expected to fall further. That means evaluations could take longer, driving up costs.

Unannounced Audits

Notified Bodies will be required to conduct unannounced audits of manufacturers and suppliers to ensure that all participants in the device development process are following the new regulations. This requirement also will mean higher costs for manufacturers.

Scrutiny Process

A new provision allows authorities to take a second look at technical documentation prior to CE approval of high-risk devices. Article 44 will require the NB to submit a new technical review report, allowing authorities to request further information — potentially delaying submissions by several months, thereby reducing the market advantage of introducing products in Europe first.

Classification Changes

There will be changes in product classification. The impact will be especially pronounced for in vitro diagnostic devices, which will be redesignated from Class A, signifying lowest risk, to Class D, highest risk — with NBs required to take part in evaluating all but Class A devices. That means NBs will participate in about 80% of IVD classifications versus 20% today. This accounts for the extended 5-year transition period for the new IVD regulations.

Companion Diagnostic Designation

Companion diagnostics will be assigned a new Class C designation under the new rule, and therefore will face regulation for the first time under the in vitro device regulation — a change that means mandatory involvement of competent authorities. Under the current regulatory system, most companion diagnostic tests are classified in the lowest risk category and are thus self-certified.

Stricter Requirements for Comparative Evaluation

It will be much more challenging to demonstrate product safety and performance using equivalence data. The new rules require more data, and it will be more rigorously interpreted. Additionally, a manufacturer performing a comparative evaluation must obtain agreement from the company whose device it is using as the basis of comparison, further complicating the process.

Technical Documentation

Until now, there was no prescribed way of providing data to NBs, leaving each device maker to produce technical files to its own standards. The new rules are much more specific concerning the content and format of technical files, so it's likely that all product and product family files will require some conversion.

POSITIVE INDUSTRY REACTION

Challenges aside, industry groups have embraced the changes. "The European medical device industry recognizes that Europe's regulatory framework needs an overhaul to strengthen the system that has been, up until this point, the world's fastest in providing life-saving technologies without compromising safety," the trade association MedTech Europe said in a statement on its website.

"The rules must be fit for purpose, more transparent, and better adapted to scientific and technological progress," the organization continued. "MedTech Europe supports revised legislation that speeds up approval processes, strengthens harmonized standards, and creates an integrated approach that is better coordinated and managed."

Likewise supportive is GS1 UK, part of the global non-profit organization GS1, which develops and maintains global standards for business communication. Manufacturers will use GS1 global standards to implement the new EU system of Unique Device Identification, which aims to support patient safety and supply-chain security.

"Using GS1 standards for UDI benefits patients, the healthcare system, and the medical device industry," said Glen Hodgson, Head of Healthcare for GS1 UK. "We're working with healthcare organizations to help them identify medical devices, which will help make recalls quicker and

more efficient — particularly compared to the often incomplete paper-based systems often used today."

GS1 standards for UDI provide the foundation for a secure global healthcare supply chain by recording accurate data for adverse events and documenting the use of medical devices in electronic health records and clinical information systems, Hodgson said. "This is a huge step forward for patient safety in the U.K."

WHAT SHOULD YOU DO NOW?

OK, but these regulations are phasing in over a period of years, so there's lots of time to prepare — right? Wrong! In fact, it would be hard to overstate the importance of early, thorough, and careful preparation. Close attention to preparation and planning are essential, starting now, because in some cases, time is shorter than it might appear. For example, all NBs need to be reaccredited, a process than can start 6 months after the official texts are published — a process that's planned to take about a year. That means NBs won't be ready for auditing until 2019, cutting roughly in half the 3-year transition period.

We're advising our customers to make full use of the 3- and 5-year transitions, avoiding the temptation to conduct business as usual and play catch-up as the final implementation dates draw closer. In particular, companies that are in the process of improving an existing device must perform a gap analysis to determine if a literature-based clinical evaluation will suffice, or if the revised product will require evidence derived from a clinical investigation.

There are many other things to start considering:

- If you don't already have them, develop standard operating practices and processes to support successful inspections and audits

- Train staff to conduct mock audits and provide tools for ad hoc preparation. This will go a long way to instill in your organization a culture of attention to detail that's essential to maintaining an audit-ready environment

- Makers of CE-marked devices will need to update some processes and procedures, especially concerning post-market surveillance and clinical follow-up, between now and 2020

- As discussed, the new rules require recertification of all NBs. Will your current NB still be appropriate for your needs? With the number of NBs expected to decline, finding an organization that's up to the task could be difficult.

- Longer evaluations dictated by the new regulations will drive up assessment costs, possibly delaying product release. That will, at minimum, affect cash flow — and for small and virtual pharma and biotech companies, it could be an existential threat.

- New technical documentation standards will affect nearly everyone. What's involved, and how long will it take? Will you need additional staffing?

- If you're required to conduct clinical studies in place of the literature reviews that previously sufficed, are you equipped to do so? Would engaging a contract research organization be more effective than undertaking this lengthy and costly process on your own?

Through its new approach to device regulation, the EU has taken laudable and prudent steps to acknowledge that patient outcomes and safety are our primary goals — but the transition will not be an easy one for device makers. The phase-in clock has just started ticking, and manufacturers should make good use of the next few years to embrace the new regulations for the good of the device industry, and ultimately for the benefit of the patients it serves. ◆

BIOGRAPHY

Joanne Emmett is VP, Medical Devices, at Premier Research, overseeing teams around the world, ensuring that each of the company's teams is made up of the right people at the right time with the right skills to advance new and creative drug and device development practices. Working with Premier Research resources and customers, she makes certain that their personalities and work styles are thoroughly compatible with those of the client. Her past operational experience within large and small CROs brings to Premier Research a strong and diverse skill set focused on customer service.

CLINICAL TRIALS

Why Are Metrics Important in Starting Clinical Trials?

By: Craig Morgan

INTRODUCTION

This question may seem counter intuitive, as we are exposed almost daily to the dire performance of clinical trials and their spiraling costs resulting from incurred delays. According to a recent study by KPMG,[1] within the pharmaceutical industry, the return on R&D expenditure has fallen from an industry average of approximately 20% 20 years ago, to 10% now, with the average cost of developing a drug rising during that period at a rate 7.4% higher than inflation, with the increasing costs of conducting clinical trials responsible for most of this increase.[2] It is estimated that it now costs upward of $2 billion dollars to bring a new drug to market.[3]

And perhaps most distributing is the fact that cycle time associated with starting clinical trials, ie, steps involved in study startup (SSU), such as, the selection of investigate sites at which to conduct the study, and activation of the site to receive first subject, have not changed in more than 2 decades.[4] According to the Tufts Center for the Study of Drug Development (CSDD), 37% of sites selected for clinical trial studies under-enroll, and 11% fail to enroll a single subject. Eventually, 89% of studies meet enrollment goals, but often at the expense of sponsors faced with doubling the original timeline due to poor enrollment.[5] At a time when it takes an estimated 8 months to move from pre-visit through to site initiation,[6] with the associated cost of initiating one site ranging from $20,000 to $30,000.[7] Overall, poor site selection, the inability of sites to predict the rate of enrollment, and the subsequent need for study rescue may increase cost of trials by 20% or more.[8]

Against this backdrop, it is clear that metrics are indeed critical to efforts to rein in clinical trials that are either poorly initiated or have incurred unforeseen events, which place the original timelines and/or budgets at risk of overages. They also drive competitive performance among those organizations performing trials.

LEVERAGING BUSINESS INTELLIGENCE IN CLINICAL TRIALS

Metrics provide the foundation for business intelligence (BI), affording clinical research teams an opportunity to intervene before the effects of a risk have been occurred. Risk mitigation is therefore optimal, using systems that can provide timely, preferably real-time data on trial bottlenecks, which indicate red flags to be reviewed and addressed or at least tracked carefully throughout the trial.

BI has become an increasingly popular topic in clinical trials as clinical project managers[9] are expected to make smarter decisions on intelligence derived from clinical trial data, and sponsors/contract research organizations (CROs) are looking for ways to incorporate BI into the eClinical systems they are using to empower oversight — turning raw trial data into actionable information.

By 2020[10] 72% of clinical trials are anticipated to be outsourced, up from just 23% in 2012. With this in mind, technology that can provide sponsors with real-time insights into clinical operations is essential. This technology should also provide CROs with automated alerts for workflows and sponsors with multiple reporting options, including on-demand static reports, snap-shot reports with status data that can be manipulated for further analy-

"By 2020 72% of clinical trials are anticipated to be outsourced, up from just 23% in 2012. With this in mind, technology that can provide sponsors with real-time insights into clinical operations is essential. This technology should also provide CROs with automated alerts for workflows and sponsors with multiple reporting options, including on-demand static reports, snap-shot reports with status data that can be manipulated for further analysis, and full access."

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Having technology that can automate or assist in the timely monitoring of trials is a significant improvement over the current "status quo" of manual methods, such as spreadsheets, which are cumbersome and erroneous, not to mention only provide a dated snap-shot of trial performance.

BUT HOW DO METRICS DRIVE PERFORMANCE COMPETITIVENESS?

Benchmarking of trial data allows clinical research teams to gauge their performance and progress against internal data, as well as externally run trials. It allows them to see at a glance if they are on par with past trials the organization has run of a similar size, geographic footprint, therapeutic area, indication, etc. If not, why not? But equally as important, and maybe arguably more so, is how is the clinical research team performing against other organizations? This is particularly important in the case of a CRO vying for a pharma outsourced study contract or for pharma's needing to justify the continued outsourcing relationship. A review of benchmarking data may indicate red flags not otherwise raised during the monitoring of the trial, and may be country specific. But benchmarking is not without its challenges.

"Benchmarks should be generated from standardized, well-conceived data elements and performance metrics," said Linda Sullivan, Co-founder and President at the industry group Metrics Champion Consortium. "Additionally, the data needs to have sufficient metadata associated with it so you can make meaningful comparisons and correlate benchmark results with best practice outcomes."

From an internal perspective, organizations can capture cycle-time metrics on whichever artifacts they deem important to measure, and as long as these metrics have clear definitions and are measured consistently between trials, then these measurements become internal benchmarks, upon which future trials can be gauged. But for external purposes, allowing organizations to gauge performance against one another, clear, consistent, and concise industry-wide standards are required. This ensures a true "apples to apples" comparison that has the added benefit of improving trial data quality, because data that might not have been previously recorded, such as certain start or stop dates, is now required. Negative cycle times or cycle times that are outliers should be reviewed to ensure accurate data entry.

With standards in place that can be

FIGURE 1

FIGURE 2

applied across all studies, global milestones need to be utilized. Global milestones are important because they recognize that the nomenclature of artifact naming conventions is not consist across organizations, or even countries, and nor will it ever be. For example, these are dependent on an organization's SOPs in which the events Activated, IP Release, and Site Initiated could be synonymous. Nevertheless, what is important is that these cycle-time metrics can be accurately measured and mapped to an industry defined standard.

Applying industry standards and global milestones for clinical and operational data, the goal of external benchmarking in clinical trials is achievable. But is this the end of the story? No, in reality it is just the beginning…

MOVING BEYOND OPERATIONAL & REGULATORY METRICS

Benchmarking allows for gamification, which could be extended beyond country or CRO (if the trial is outsourced to multiple vendors) to be based on role assignment, with associated financial incentives. Some might view this option as unethical or raise questions of quality, of individuals potentially gaming the system to reap the rewards and accolades of exceeding the threshold of industry performance for their position. But nevertheless, it is a logical progression, and many of these arguments don't carry much weight in a system with numerous checks and balances. Moreover, it allows for greater transparency in the process of conducting clinical trials and would allow management the opportunity to highlight those Clinical Research Associates (CRAs) and others that are star performers.

Gamification in the pharmaceutical industry has been used to improve relationships with patients by using games to encourage disease management, with Sanofi[11], Boehringer Ingleheim, and Eli Lilly[12], developing apps. In the context of clinical trials, gamification presents an excellent opportunity to improve performance and reduce costs. There are a number of areas that hold promise, including patient recruitment, patient and key clinical staff retention, disease research, investigator and site training, and improving site performance.

Sponsors and CROs are looking to innovative methods to improve site performance, such as rewarding sites with badges as they pass certain predetermined milestones (eg, 10 patients screened, all training completed) or using leaderboards to show sites how they are performing relative to their peers. Principal investigators are motivated by watching their site on the leaderboard to see how they rank on key metrics, such as patient enrollment and data query resolution. Meanwhile, exposing clinical operations teams to metrics, leaderboards, and other activities as they undertake their daily work can potentially improve both performance and quality. And inspiring friendly competition can motivate global site performance areas, such as activation, patient enrollment, and more.

Take the case of T.J. Sharpe. Faced with the prospect of a Stage IV Melanoma diagnosis back in 2012, he vowed to never give up, determined to see his two young children grow up with a father. Working with his oncology team, T.J. identified the best possible treatment option, which at the time came in the form of a promising immunotherapy clinical trial nearly 4 hours away from his home. After packing up his family and relocating to Tampa, he learned shortly after his arrival that the trial was delayed due to a pending signature on a clinical trial agreement (CTA), a contract. Without the luxury of time on his side, T.J.'s new oncologist suggested that he may have to consider "plan B." Determined not to let a document sitting on someone's desk get in the way of a potentially life-saving treatment for him or for other patients in the study, T.J. got to work. After a long process, which involved contacting the trial sponsor, finding the

right person, and telling his story, the study team resolved the startup hurdle in a timely enough manner for T.J. to receive treatment. After a long journey, which included participation in a second clinical trial, today, T.J. is in remission and healthier than ever. T.J.'s story is regrettably all too common – incentives could reduce these unnecessary delays.

Benchmarking would also allow for efficient resource allocation. A review of subpar performance may indicate that this is simply due to staffing issues, affording executives the option of either allocating more staff to critical steps in the progress, called crashing the schedule[13] in project management terminology or opting to incur the subsequent financial ramifications from a delayed launch to the market. Ultimately, sponsors stand to lose up to $8 million daily due to a trial delaying a product's development and launch.[14]

Lastly, benchmarking is the precursor to predicative analytics or forecasting, enabling clinical research teams to estimate future outcomes based on their current state of progress. This is critical to risk mitigation and a preemptive weapon in the fight against the dreaded rescue study.

INDUSTRY-DRIVEN ADOPTION

CROs, often seen as the bastions of innovation in clinical trials, are leading this charge into the BI foray. Top CROs have been aggressively acquiring data sources to leverage in data mining. In 2013, PPD acquired Acurian[15] to gain analytics-driven feasibility capabilities, LabCorp acquired Covance[16] for collective data resources to drive greater R&D productivity, and Quintiles merged with IMS Health[17] last year to improve clinical trial execution using patient data.

Informatics is the new frontier in their innovative efforts, as they look to gain insights in operational data to drive improvements via targeted enrollment efforts. A theme that was central to the recent Disrupting Clinical Operations from the CRO Perspective[18] presentation at DPharm 2016 by top level CRO executives. What is the common thread? We now operate in a data-driven environment. Follow T.J.'s story at www.philly.com/patient1/.◆

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BIOGRAPHY

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

TECHNOLOGY-ENABLED HEALTH

Digitally Connected Health Technologies: Blazing Meaningful Trails in Healthcare

By: Daniel Spors and Kyle Dolbow, PhD

INTRODUCTION

A new age is dawning in healthcare. Patient-centered care has become the driving force behind everything from healthcare legislation (such as MACRA and MIPS), payment models (ACOs and P4P models), to changes in the care delivery structure (think eHealth and telemedicine), and the management of chronic and complex conditions. The latter, which accounts for 81% of all hospital admissions, 91% of prescriptions filled, and 76% of doctor visits, is at the very core of an emerging market known as digitally connected health technologies.

The overall digital health market is currently $76 billion, and is estimated to grow at 21%. This space includes life sciences companies and medical device companies that are incorporating digital technology into their products and services, such as smart inhalers and remote therapy devices, which can provide data about how and if patients are adhering with prescribed care plans and medications. When done correctly, this data can be used to reduce the incidence of costly complications and improve health outcomes. And that benefits everyone.

START BY ASKING THE RIGHT QUESTIONS

An effective connected health program starts with answering some important questions, such as: What is the benefit of digitally connected programs to our organization? How do we systematically introduce connectedness into our products and services? How will we leverage this investment in our marketing and competitive strategy? What assets and resources are required to implement and support the connected health program? Are our partners aligned in a sustainable strategy and approach?

SUCCESS COMES IN MANY FORMS

For life sciences and medical device companies, an investment in digital health has short- and long-term business benefits. For example:

- Business impacts, such as increased sales, competitive positioning, and operational efficiencies;
- Impacts on the care process, such as improving adherence, care management decisions, and enabling process efficiencies;
- Improving patient outcomes, such as increased loyalty, satisfaction or preference, better health outcomes, or behavior change and improved quality of life;
- Clinical impacts, such as the ability to inform the care decision process, and to optimize their costs/revenue; and
- Impacts on the total cost of care and outcomes, including adherence, reduction in complications, participation in shared-risk contract opportunities, and expanded market access.

There is one, common denominator for all healthcare companies with a connected health program: the need to generate

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real-world results. Real-world results include data that demonstrate a product's ability to improve outcomes and lower costs outside of a clinical research setting or allow the same outcomes to be achieved in a more effective way. In other words, outcomes from real patients in real healthcare situations.

For example, imagine the benefit of knowing not only how many times patients with asthma or COPD (chronic obstructive pulmonary disease) used their inhalers, but how much of the medication was successfully received and when the medication was dispensed.

When sending a patient home following a clinical procedure, imagine the difference in follow-up care if nursing professionals could remotely monitor their status and adherence with wound care, antibiotics, or pain management. And just think of the reduction in emergency department visits if an entire care team and patient support system could be digitally connected to help people with complex or chronic conditions maintain an optimal lifestyle.

Once you define what success looks like for your company, there are several factors that will determine your ability to achieve the targeted outcomes within the desired timeframe. In addition to delivering a product that produces optimal results, there's the sticky matter of getting said product into the hands of the right end-users and embedding it into a value-based contracting and payment system.

ENSURE YOUR SUCCESS WITH A PROVEN ROADMAP

Once you've addressed the core strategic questions and success metrics, you can ensure your success by following a proven roadmap that helps you identify the opportunities, challenges, and risks for your organization, as well as factors you need to address to mitigate risks. Some of the most common challenges for implementing a digitally connected health program include:

- Capturing device-generated and patient-generated data
- Data security, privacy, and governance
- Management and metrics
- ROI models and cost
- Payment and reimbursement
- Predictability of outcomes
- Packaging
- Existing and forthcoming government regulations

Approach these factors wisely and with a clear eye on both initial and long-

FIGURE 1

inCourage Airway Clearance Therapy by RespirTech

term success, as well as your ongoing pathway to manage growth, costs, risks, and opportunities. The initial decisions and infrastructure partners you choose can make a big difference between an ongoing program that produces sustained results, or a series of experiments that show promise, but never make the jump to meaningful results. Evaluate your options to ensure the right balance between your market opportunity and the needs of your organization, today and in the future.

DIGITALLY CONNECTED HEALTH CARE FOR RESPIRATORY THERAPY

Cystic fibrosis (CF) and COPD are two complex respiratory conditions that require ongoing monitoring because patient adherence with medication and therapy regimens can impact a patient's stability and help slow the progression of these conditions. RespirTech is a Minnesota-based manufacturer of medical devices designed to improve airway clearance therapy for patients with these and other respiratory conditions.

The inCourage® Airway Clearance Therapy system (Figure 1) features a therapy vest that delivers air pulses and chest compressions to loosen and move mucus from the airways of people with cystic fibrosis and bronchiectasis, a common underlying condition of COPD. The comfort, ease of use, and emerging connected capabilities of the inCourage System are designed to enhance adherence by patients, which in turn, can improve clinical outcomes.

RespirTech and HealthFactors began working to expand the capabilities of RespirTech's inCourage System to capture therapy information useful for patients, families, and healthcare providers. The company aims to provide more timely and complete therapy information to contribute to improved care management and lower overall disease costs.

Today, RespirTech's Bluetooth-enabled system is capable of connecting to both cellular and Wi-Fi networks; securely transferring data from patients' inCourage Systems to doctors, caregivers, and device support staff; and implementing ongoing data security and compliance updates. In addition, a related mobile application is easy and convenient for patients and their families to use and manage. The company is currently gathering and evaluating real-world evidence on the digitally connected airway clearance system's ability to enhance patient adherence and overall care.

A rapidly expanding area in respiratory therapy is smart inhalers and their use in the treatment of COPD and asthma to assess and manage the effectiveness of prescription medications for patients. Collaborations are emerging that focus on several clinical and technology advancements needed to implement these treatment solutions into mainstream clinical practice. Look for continued activity in this area from a variety of healthcare stakeholders in the coming months. ◆

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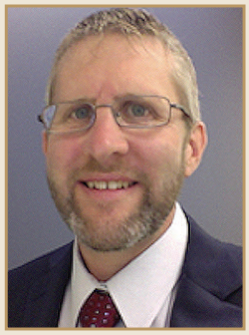
BIOGRAPHIES



Daniel Spors is Chief Commercial Officer at HealthFactors, Inc. As a founding member of HealthFactors and Preventice, he has led and participated in the development and rollout of a variety of healthcare programs over the past 14 years of his 24-year career. Prior to HealthFactors, he held staff and leadership positions at Preventice, IBM, ShowCase Corporation, and Centerfield Technology.

Dr. Kyle Dolbow is Chief Executive Officer at HealthFactors, Inc. Prior to HealthFactors, he was a pioneer at Preventice, a company focused on remote cardiac monitoring and integration into health management. He also served as President of Vree Health, an innovative subsidiary of Merck, Sharp & Dohme Corp., which focuses on bringing new technology-enabled services to the healthcare market. HealthFactors creates outcomes-based, therapy-specific care management programs using digitally connected health technologies. The company's technology, expertise, and proven processes help life sciences and medical device companies improve health for people with chronic or complex conditions. Dr. Dolbow earned his PhD in Chemistry from MIT.

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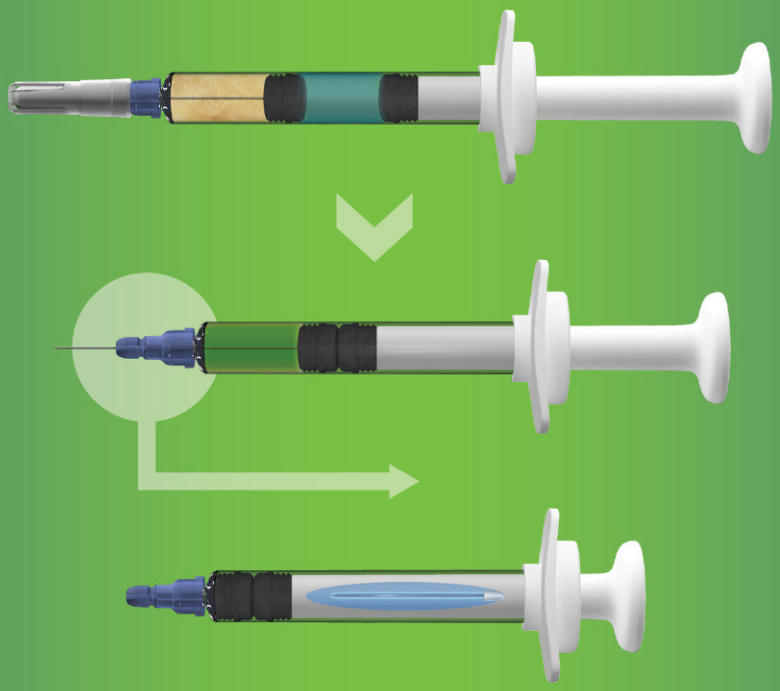

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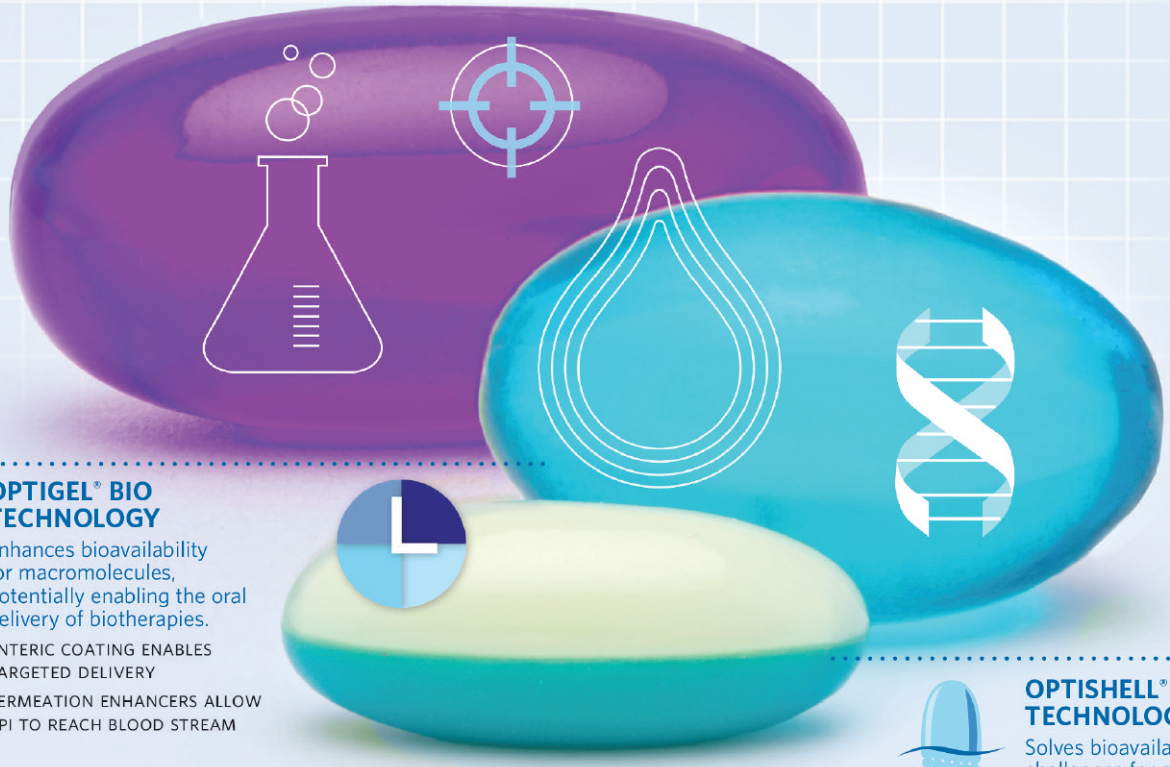

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