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Drug Development & Delivery

September 2016 Vol 16 No 7 www.drug-dev.com

Injection Technologies: Market Drivers & Innovative Design

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

IN THIS ISSUE

INTERVIEW WITH **ALCAMI'S** CEO, PRESIDENT & CHAIRMAN DR. STEPHAN KUTZER

Anthony Recupero, PhD
Designed With Patients in Mind: The Art of Patient-Centric Drug Formulation

Cindy Dubin
Injectable Drug Delivery: Key Trends Define Device Design Now & in the Future

Ronak Savla, PhD
Lipid-Based Drug Delivery System to Bring Poorly Soluble Drugs to Market

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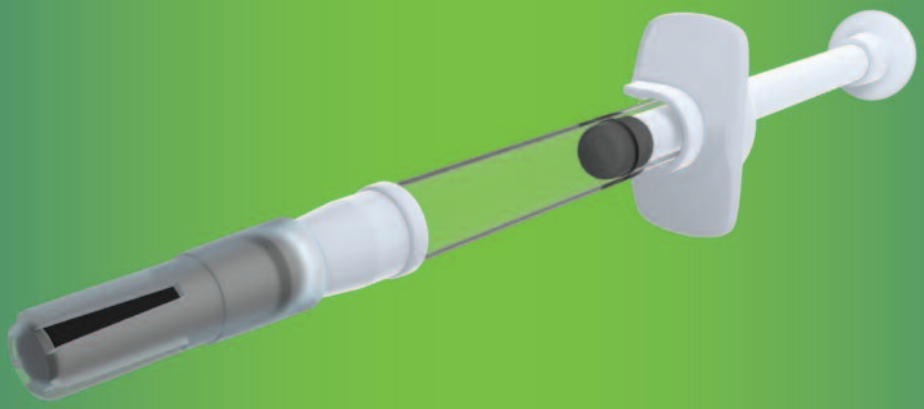

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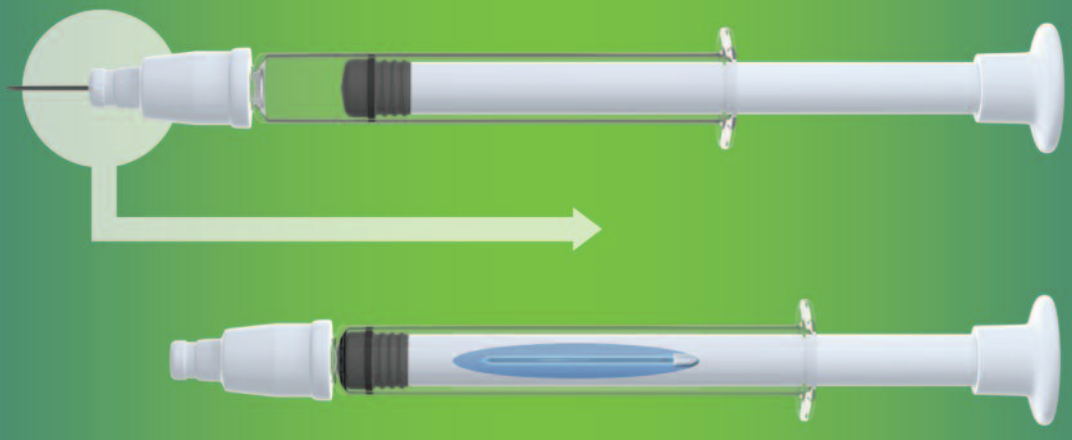

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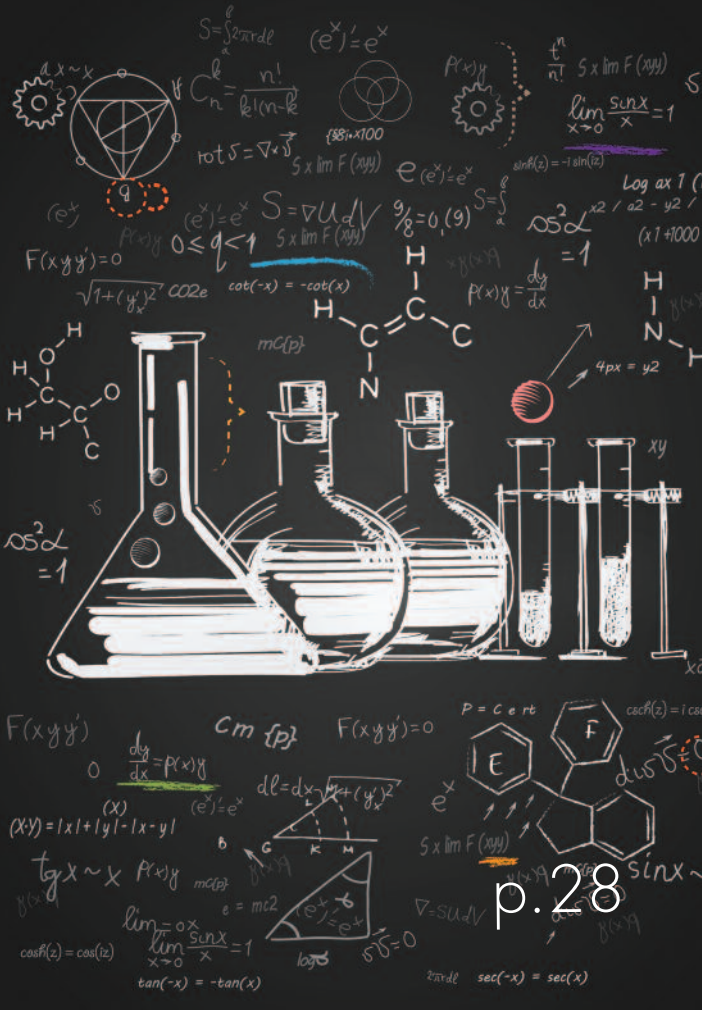

Table of Contents

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Injection Technologies

"The global injectable drug delivery devices market is expected to increase from around $11.6 billion in 2013 to around $ 17.5 billion in 2018. Growth is being attributed to the rising prevalence of chronic diseases, the biologics market, technological advancements, and demand for self-injection devices, which are expected to experience the highest growth rate of 16.1%."

p.50

Table of Contents

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Audentes Therapeutics Announces First Patient Enrolled in the INCEPTUS Study

Audentes Therapeutics, Inc. recently announced that the first patient has been enrolled in INCEPTUS, a prospective study designed to characterize the disease presentation in children living with X-Linked Myotubular Myopathy (XLMTM). The study is evaluating subjects prior to potential enrollment in ASPIRO, the planned Phase I/II clinical study intended to evaluate the safety and preliminary efficacy of AT132, the Audentes product candidate for treatment of XLMTM.

"The initiation of enrollment for INCEPTUS is an important first step in the clinical development of AT132 for the treatment of XLMTM and a notable milestone for Audentes," said Dr. Suyash Prasad, Audentes' Senior Vice President and Chief Medical Officer. "The burden of the disease of XLMTM to children and families is considerable, and we are grateful to those who have agreed to participate in the study."

INCEPTUS is an international study of boys with XLMTM, ages three years or younger, designed to characterize their individual disease presentation, with a specific focus on respiratory measurements and assessment of muscle strength and function. Patients enrolled in INCEPTUS will be evaluated over a three to twelve-month period prior to their potential participation in ASPIRO. INCEPTUS is designed to serve as a longitudinal baseline and within-patient control for subjects who enroll in the ASPIRO study, while also facilitating the operational aspects of ASPIRO once initiated.

Audentes plans to file investigational new drug applications for AT132 with North American and European regulatory authorities in the first quarter of 2017. The company expects preliminary data from the ASPIRO study in the fourth quarter of 2017. For additional information on INCEPTUS, please visit www.clinicaltrials.gov.

X-Linked Myotubular Myopathy (XLMTM) is a rare, inherited disorder characterized by severe muscle weakness, respiratory impairment, and early mortality. There is no approved treatment for the condition. It is caused by mutations in the MTM1 gene, which encodes a protein called myotubularin. Myotubularin plays an important role in the development, maintenance, and function of skeletal muscle cells. XLMTM affects approximately 1 in 50,000 newborn males worldwide. Audentes is developing AT132 for the treatment of XLMTM in collaboration with Genethon (www.genethon.fr). AT132 is a novel product based on AAV gene therapy technology.

Audentes Therapeutics is a biotechnology company focused on developing and commercializing gene therapy products for patients living with serious, life-threatening rare diseases. The company has four products in development, AT132 for the treatment of X-Linked Myotubular Myopathy (XLMTM), AT342 for the treatment of Crigler-Najjar Syndrome, AT982 for the treatment of Pompe disease, and AT307 for the treatment of the CASQ2 subtype of Catecholaminergic Polymorphic Ventricular Tachycardia (CASQ2-CPVT).

Catalent Biologics & Zumutor Collaborate to Develop Antibodies With Enhanced ADCC Activity

Catalent Pharma Solutions and Zumutor Biologics Inc. recently announced a successful research study, combining Catalent's proprietary GPEx technology and Zumutor's fucose knockout platform, to create new and more efficacious antibodies.

The GPEx technology platform creates stable, high-yielding mammalian cell lines for even the most difficult-to-express proteins. The advantages of applying GPEx technology span from early feasibility studies and clinical manufacturing, to commercial- scale production.

Working in partnership, Catalent and Zumutor have created a fucose knockout GPEx cell line expressing high levels of an anti-HER2 antibody. The resulting modification completely removes fucose from the antibody, resulting in greatly enhanced Antibody Dependent Cellular Cytotoxicity (ADCC) without impacting production levels. The study was conducted in Zumutor's research and development facility in Asia.

"Zumutor's fucose knockout technology enables us to create new and more efficacious antibodies. The inherent stability of GPEx cell lines makes these modifications possible and allows GPEx cell lines to be modified quickly, to produce a more potent antibody. Our partners have the potential to leverage this improved technology in therapeutic antibody product development, and generate a new regime of drug products engineered toward patient benefits," said Kavitha Iyer, Chief Operating Officer of Zumutor.

"GPEx technology was designed to offer our partners advantages over conventional cell line engineering systems, including increased flexibility and higher, more stable yields," added Mike Riley, Vice President & General Manager of Catalent Biologics. "The use of GPEx technology, in combination with Zumutor's afucosylation platform, has shown exciting results, and has the potential to be applied to other antibodies that could benefit from ADCC enhancement as part of their development programs."

Catalent's proprietary GPEx technology creates stable, high-yielding mammalian cell lines with high speed and efficiency. The advantages of applying GPEx technology span from early feasibility studies, to clinical manufacturing, through to commercial-scale production. To date, seven GPEx-based antibody and protein products are approved and marketed, and 34 therapeutic candidates are currently in the clinic across the world.

Catalent performs GPEx programs at its state-of-the-art biomanufacturing facility in Madison, WI, which was completed in June 2013. Designed for flexible cGMP production from 10 L up to 1,000 L, and non-GMP production up to 250 L, the site features extensive single-use technologies and unidirectional flow to maximize efficiency and safety.

Catalent is the leading global provider of advanced delivery technologies and development solutions for drugs, biologics, and consumer health products. With over 80 years serving the industry, Catalent has proven expertise in bringing more customer products to market faster, enhancing product performance and ensuring reliable clinical and commercial product supply. For more information, visit www.catalent.com.

Piramal Enterprises Enters Agreement to Acquire Ash Stevens

Piramal Enterprises Limited recently announced that its wholly owned subsidiary in the US has entered into an agreement to acquire 100% stake in Ash Stevens Inc., a US-based Contract Development and Manufacturing Organization (CDMO), in an all cash deal for a consideration of $42.95 million plus an earn-out consideration capped at $10 million. This potential transaction is expected to be completed by the end of August.

Located in Riverview, MI, Ash Stevens has over 50 years of experience in contract manufacturing, and serves several biotech, mid-size pharma, and large pharmaceutical clients worldwide.

With over 60,000 sq ft of facilities, eight chemical drug development and production laboratories, and six full-scale production areas, Ash Stevens has built a stellar reputation, led by science, driven by operational excellence, and one that emphasizes quality as a culture. As one of the leaders in HPAPI manufacture, Ash Stevens has an impeccable safety record of working with high potency anti-cancer agents and other highly potent therapeutics. The state-of-the-art manufacturing facility in Michigan features all necessary engineering and containment controls for the safe handling and cGMP manufacture of small and large-scale HPAPIs, with Occupational Exposure Limits (OELs) ≤ 0.1µg/m3. The facility has approvals from US, EU, Australia, Japan, Korea, and Mexico regulatory agencies.

"The acquisition of Ash Stevens fits well with our strategy to build an asset platform that offers value to our partners and collaborators. Currently, around 25% of the molecules in clinical development are potent. Our clients are looking for reliable partners that can assist them in advancing these programs forward," said Vivek Sharma, CEO of Piramal Pharma Solutions. "North America is a key market that we can now service with our three local facilities - the Coldstream Labs in Kentucky for fill finish needs, the Torcan facility in Toronto for complex high value APIs and now, Ash Stevens in Michigan for HPAPIs. Having facilities with a differentiated platform and geographical proximity to clients are keys toward building strategic partnerships. We expect this acquisition to also be synergistic with our Antibody Drug Conjugates (ADCs) and injectable business. We can now fulfill client requirements for a single source of supply for both high potent APIs and drug products."

"With its rich history of scientific excellence, a track record of 12 product launches, Ash Stevens is well poised to become the partner of choice for clients looking to advance programs from early development through launch. In addition to the business benefits that the combined entity will bring to our clients, I am also pleased that the firms share common core values: both were founded by successful entrepreneurs, value integrity, and are committed to a customer-first approach," added Dr. Mark Cassidy, President of the API Business at Piramal Pharma Solutions, "I am pleased to welcome the Ash Stevens team into the Piramal group. We expect them to be an integral part of our future growth plans."

"We look forward to working with the Piramal leadership and management team, to develop API solutions that benefit customers and improve the lives of patients. The commitment that Piramal has shown toward growing its healthcare businesses, coupled with the complementary capabilities that our two firms have, makes this an exciting time for Ash Stevens and our employees. We have already identified areas where we can create significant value together, and will be moving forward rapidly to achieve those objectives," said Dr. Stephen Munk, CEO of Ash Stevens.

The Piramal Group, led by Ajay Piramal, is one of India's foremost business conglomerates with a global footprint. With operations in 30 countries and brand presence in over 100 countries, the Group's turnover is around $1.3 billion in FY2016. The Group's diversified portfolio includes presence in industries like healthcare, financial services, healthcare information management, glass packaging and real estate. Driven by the core values of knowledge, action and care, the Group steadfastly pursues inclusive growth, while adhering to ethical and value driven practices. Piramal Foundation, the philanthropic arm, has initiatives running across healthcare, water, education and women empowerment in 19 states of India. For more information, visit www.piramal.com.

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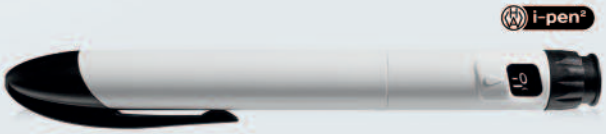

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Allergan Sales to Consolidate Four New Jersey Locations

The state Economic Development Authority approved Allergan's application for Grow NJ tax breaks that it said would keep 1,019 workers in the state, and add 300 full-time jobs. Allergan has operations in Parsippany, Jersey City, Rockaway, and Bridgewater. It wants to consolidate those operations, and is considering two sites: a 431,500-sq-ft site in Madison, or a 344,280-sq-ft location in Lansdale, PA.

If the company chooses the Madison site, Allergan is expected to invest more than $103 million at Giralda Farms in Madison, site of the former estate of Geraldine Rockefeller Dodge. The EDA says keeping Allergan in New Jersey is expected to bring a net benefit to the state of more than $384 million over 20 years.

To take advantage of the Grow NJ tax breaks, Allergan would have to give up $15.2 million in tax incentives earlier awarded to its subsidiaries Forest Laboratories Inc. of Jersey City and Watson Pharmaceuticals Inc. of Parsippany, the EDA said. Allergan has more than 7,500 employees in 20 locations in the United States.

"Allergan is a significant employer in New Jersey, and its presence adds to the state's leadership in the pharmaceutical sector," EDA Chief Executive Officer Melissa Orsen said.

The EDA also approved a 10-year Grow NJ grant for PsychoGenics Inc., which is based in Tarrytown, NY, and has a laboratory in Montvale, NJ, that employs 35 workers. The company applied to the EDA for the tax break to consolidate its operations into a 65,000-sq-ft site at an existing building at 215 College Road in Paramus, NJ.

That move would keep 35 workers in New Jersey and add 82 full-time jobs, with a median annual salary of about $83,200, the EDA said. In addition, PsychoGenics would invest $5.55 million in the new site, including the construction of office and laboratory space.

The state grant would come to $373,125 a year for 10 years. The net economic benefit to the state is estimated at more than $22.4 million over 20 years, according to the EDA.

PsychoGenics also is considering a site in Pearl River, NY. The company did not return calls seeking comment. PsychoGenics was founded in 1999 and provides testing services to pharmaceutical researchers specializing in treatment of neurological disorders, such as Alzheimer's disease, Parkinson's disease, schizophrenia, and autism spectrum disorders.

Economic development officials say that state tax incentives are necessary to compete with other states in the fight to keep and create jobs. But the tax breaks have drawn criticism from NJ Policy Perspective, a progressive group, which says that they drain money from important public programs, including education and transportation, that are needed to grow New Jersey's economy.

Portola Pharmaceuticals Receives Complete Response Letter From FDA

Portola Pharmaceuticals Inc. recently announced it has received a Complete Response Letter (CRL) from the US FDA regarding its Biologics License Application (BLA) for AndexXa (andexanet alfa). An FDA-designated Breakthrough Therapy, AndexXa is in development for patients treated with a direct (apixaban, rivaroxaban, or edoxaban) or indirect (enoxaparin) Factor Xa inhibitor when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Currently, there is no FDA-approved antidote for Factor Xa inhibitors.

In the CRL for AndexXa, the FDA requested that Portola provide additional information primarily related to manufacturing. The agency also asked for additional data to support inclusion of edoxaban and enoxaparin in the label, and indicated it needs to finalize its review of the clinical amendments to Portola's post-marketing commitments that recently were submitted.

Annually, 1% to 4% of patients treated with Factor Xa inhibitors may experience major bleeding, and an additional 1% may require emergency surgery. Commensurate with the increase in the use of Factor Xa inhibitors – for stroke prevention in atrial fibrillation; treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism; and prevention of DVT following knee or hip replacement surgery – the number of hospital admissions due to bleeding associated with these agents continues to grow. In the US, more than 80,000 patients treated with oral Factor Xa inhibitors were admitted to the hospital due to bleeding during 2015. Including patients taking the injectable Factor Xa inhibitor enoxaparin, it is estimated that more than 100,000 US patients could benefit from an antidote annually. Currently, there is no FDA-approved antidote for Factor Xa inhibitors for these patients.

AndexXa, an investigational drug, is a modified human Factor Xa molecule that acts as a decoy to target and sequester with high specificity both oral and injectable Factor Xa inhibitors in the blood. Once bound, the Factor Xa inhibitors are unable to bind to and inhibit native Factor Xa, thus potentially allowing for the restoration of normal hemostatic processes. AndexXa is the first compound being studied as an antidote for Factor Xa inhibitors that directly and specifically reverses anti-Factor Xa activity – the anticoagulant mechanism of these agents.

Portola's BLA for AndexXa was based on data from two Phase III ANNEXA studies that evaluated the safety and efficacy of AndexXa in reversing the anticoagulant activity of the Factor Xa inhibitors rivaroxaban and apixaban in older healthy volunteers. Results of those studies were published online by The New England Journal of Medicine in November 2015.

The BLA also included limited adjudicated efficacy and safety data from initial patients enrolled in the ongoing ANNEXA-4 study. Portola is currently evaluating AndexXa in this global, Phase IIIb/IV single-arm, open-label confirmatory study in patients receiving apixaban, rivaroxaban, edoxaban or enoxaparin who present with an acute major bleed.

The FDA granted AndexXa Orphan Drug designation, for which Portola would expect to receive seven years of marketing exclusivity if the drug is approved.

PARTICULATE IDENTIFICATION

Particle Identification for Improvement of Pharmaceutical Production

By: Kathryn A. Lee, PhD; Markus Lankers, PhD; and Oliver Valet, PhD

ABSTRACT

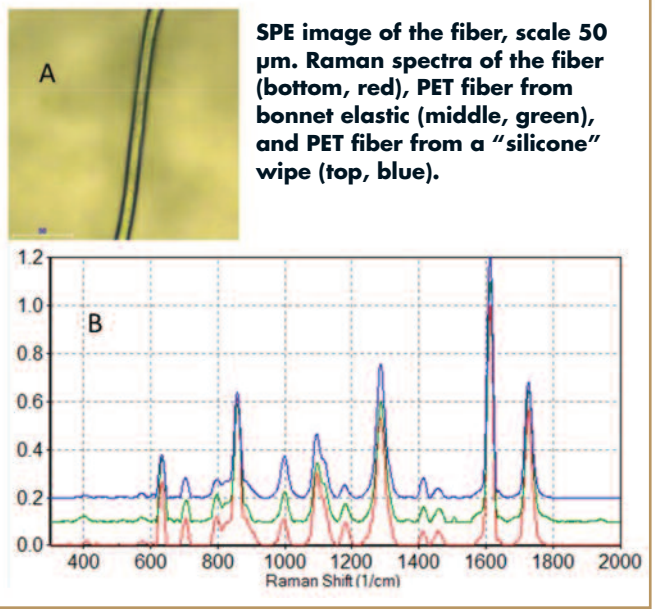
Analyses, including identification, counting, and sizing of unwanted particles in pharmaceutical products is necessary and important and can be very beneficial for product quality and process improvement because it can lead to elimination of specific particle sources. Particles can be found in products, vials, syringes, IV bags, stoppers, production equipment, swabs, scoops, and filters. Collection and preparation methods are very important to the particle analyses. The methods include washing out and filtering as well as physical separation, and must be done in clean environments to prevent contamination. For identification, it is important to consider what needs to be determined with the aspects of the various analysis techniques, including capabilities, technique complementarity, interpretation, speed, ease of analysis, accuracy, and spectral libraries. In this paper, we discuss those aspects with regard to microscopic particle counting, sizing, and identification using Raman, laser-induced breakdown (LIB), and IR spectroscopies. We discuss how those techniques can be used to accurately identify particles, and discuss important aspects to consider when using these techniques.

INTRODUCTION

Good quality of pharmaceuticals requires understanding and control of particulate matter contamination.[1,2] Particle characterization and identification in pharmaceutical production can be very beneficial for product and process improvement, and preventing product recalls.[3] Particle identification allows possible sources to be determined so that the processes can be improved to prevent unwanted particles and allows production of better quality and safer products, eliminating waste and improving throughput as well as preventing patient adverse effects.

The draft of USP <1790> focuses on detection and removal of product units that show evidence of visible particles. It promotes the need for preventing particulate contamination, which can only come from identification. "No inspection process (manual or automated) can guarantee complete

FIGURE 1



SPE image of the fiber, scale 50 µm. Raman spectra of the fiber (bottom, red), PET fiber from bonnet elastic (middle, green), and PET fiber from a "silicone" wipe (top, blue).

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removal of all visible particulate matter or other visible defects; thus, prevention of such defects is an important consideration."[4]

Analyses of particles in drugs will improve defect prevention. Analyses of particles from processing equipment will help to improve processing and cleaning. Analyses of particles on process filters can help improve processes and raw material and product specification or purification.[5] Analyses of environmental contaminants can help direct and improve personnel training and cleaning and operating procedures. Unwanted particles and materials include hair, fibers, starch, minerals, insect parts, inorganic and organic materials, microbes, stainless steel, cellulose, glass, rubber, polymers, fabrics, and lubricants, among other things. Glass and metals are most critical in terms of product recall.

This paper describes analyses of particles using filtration and manual isolation methods and identification using Raman, laser-induced breakdown (LIB), and IR spectroscopies. We provide information about the important aspects to consider when using these techniques, including capabilities, complementarity, interpretation, ease of analysis, accuracy, and spectral libraries.

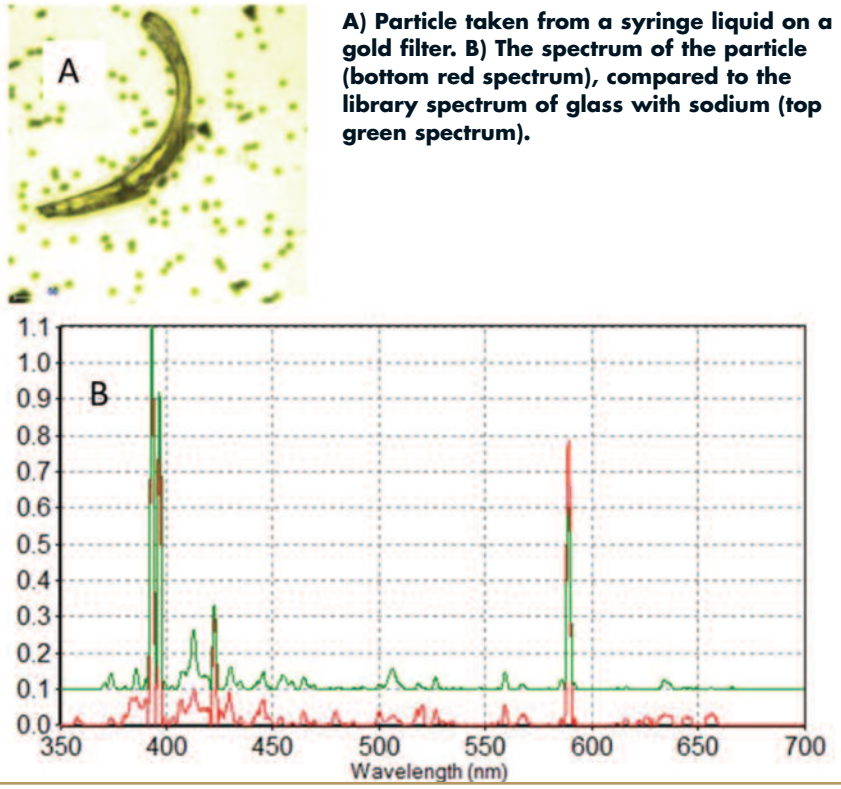
MATERIALS & METHODS

The first step of particle analysis is the reliable isolation of particles. Visible particles were removed with cleaned probes. Samples with sub-visible particles or many particles were filtered onto gold filters for direct analysis using Raman, LIBS, and IR.[6] Samples were prepared in a Laminar Flow Biohazard Hood, Heraeus Herasafe Kendro HS12 Type A/B3 Class II clean bench.

Raman and LIBS analyses were done with the Single Particle Explorer (SPE) ls metal.ID + raman.ID, manufactured by rap.ID Particle Systems GmbH. For Raman, a 785 nm laser with ≤ 50 mW was used with a spectral range of 300 to 2,000 cm^{-1} and 5 cm^{-1} resolution. For LIBS, the pulsed laser was set for 100 µJ, 3 ns. The spectral resolution was 1 nm, and the range was 350 to 800 nm. For Raman spectra, the instrument parameters were ≤ 50 mW 785 nm, spectral range 300 to 2,000 cm^{-1}, and spectral resolution 5 cm^{-1}. Standards libraries and Pearson's algorithm were used for spectral identification.

FTIR analyses were done with a Thermo Scientific Nicolet iN10 Infrared Microscope using a spectral range 4000 to 675 cm^{-1} with resolution 4 cm^{-1}. Attenuated total reflectance (ATR) spectra were taken with a Ge ATR attachment. Standards libraries and correlation searching were used.

FIGURE 2



A) Particle taken from a syringe liquid on a gold filter. B) The spectrum of the particle (bottom red spectrum), compared to the library spectrum of glass with sodium (top green spectrum).

RESULTS & DISCUSSION

Particles From Vials, Syringes & IV Bags

An example of identification of particles for root cause defect prevention was analysis of a fiber in a vial. The fiber image indicated it was smooth and not twisted, which is typical of polymer fibers, and Raman analysis indicated polyethylene terephthalate (PET). PET can have many sources, and some of the PET materials from the product supplier that were analyzed for comparison included wipes and bonnet and lab coat threads (Figure 1). Even though there were several possible sources of the fiber, identification eliminated several other

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FIGURE 3

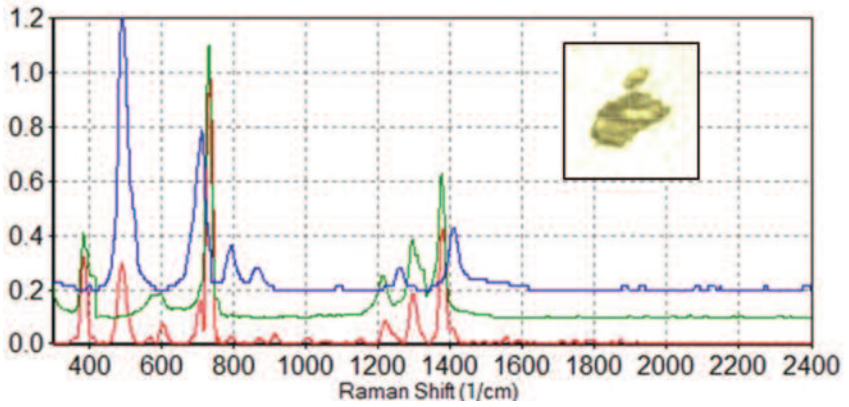

Image of a particle from a swab and Raman spectra of the particle (bottom red spectrum) compared to library spectra of polytetrafluoroethylene (PTFE) (middle green spectrum), and silicone oil (top blue spectrum).

sources of materials, such as hair or cellulose.

A particle taken from liquid from a syringe was determined using LIBS to be glass with sodium (Figure 2). Though Raman and IR can identify particles as glass, LIBS is particularly effective in determining the source of glass because it can determine the elemental composition. The physical appearance of particles can provide additional information about the source. A fiber may be from fibrous glass insulation, whereas flakes are more typical of syringe and vial glass delamination.

A primary contributor of particulate matter in vial presentations is the elastomer closure due to silicone oil on the surface.[1,7] Cellulose is a common contaminant on stoppers. Analysis by Raman and/or IR of many particles on the rubber part of a plunger taken from a filled syringe identified quartz, silicone oil, clay, protein, cellulose, and nylon. In this case, not every particle needs to be identified to confirm the stoppers were not protected from environmental contamination some time during the entire process from manufacturing of the stoppers through syringe filling. It is important to understand if the stoppers are supplied contaminated or become contaminated during the process of manufacturing of the syringes or pharmaceutical product.

IV bags and the infusion sets used to administer the contents can have particles even without any drugs added to them. Table 1 lists the sizes of the numerous particles found in two sequential 10 mL portions taken from an IV bag of 0.9% sodium chloride injection USP 50 mL through an infusion set that had a filter. The two 10-mL portions were filtered onto a gold filter for particle counting and analysis. The filter in the IV bag clearly did not prevent small particles from coming out with the liquid. The number of particles was reduced by about 40% for the second portion removed, indicating the filter may have some effect, or the particles were from the tubing below the filter.

Particles From Process Equipment

Swabs and scoops are often used to determine whether pharmaceutical processing equipment has been adequately cleaned. The particles and materials picked up on these can be analyzed by spectroscopic techniques. The particles can be analyzed directly on the devices, removed and placed on more suitable substrates, or removed into a liquid followed by filtering. Once the particles and materials are analyzed, then the process equipment cleaning protocol can be reviewed and improved to prevent process contamination from those materials. Figure 3 shows the image of a particle removed from a swab and its spectrum identifying it as polytetrafluoroethylene (PTFE) with silicone. The combination may help determine the specific source as tubing, washers, or seals. Then the process can be improved by implementing more frequent checking or changing of fittings so they do not degrade into the process.

A mass of fibers collected from a process on a scoop was analyzed and illustrates the importance of analyzing multiple areas of materials. Raman spectroscopy can analyze small areas of materials, and in this case, polypropylene with white filler as well as cellulose fibers were identified. The polypropylene with filler was consistent with beard cover fabric from that plant.

Filters

There are many types of filters used to collect particles. Figure 4 shows one example of a collodion filter, which is low-nitrated cellulose. LIBS was used to directly identify a particle on the filter as aluminum, which eliminates any steel equipment as a source.

Information Required

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"Understanding which spectroscopic identification technique to use is very important. Often, more than one technique is needed for accurate results. LIBS was shown to be useful for glass and metal identification, Raman was shown to be useful for organics and dyes, and IR was shown to be useful for material with strong dipoles. It was also shown that two techniques provided complementary information that gave more accurate identification."

Because every vial and syringe is checked for particles according to USP regulation, it is important to track the number and sizes so that it can be determined if the process is going well. An increase in the number of particles would indicate some process problem. Visible checking only consistently detects particles about 100 µm, and fibers typically have to be much longer to be detected. Knowing the sizes and identification of the particles are essential to understanding the sources, and will lead to understanding how to improve the processing. Thus, techniques that can count, size, and identify the particles should be used. Improvements can include checking and/or cleaning equipment more often, changing parts that wear out before they create particles, perhaps even changing the equipment type, improving cleaning, and better training.

IDENTIFICATION ASPECTS

Methods of Removal

There are methods for analyzing particles in situ. These can work well, but can be complicated by bubbles and contributions from the surrounding materials. Isolating the particles by filtering has the advantage of removing any materials that can interfere with the analysis. Filtering avoids manual isolation, which is difficult, time-consuming, and potentially destructive to the particles. This avoids tedious manual isolation and difficult manipulation of single particles. For filtering particles, it is important to choose a filter with the right pore size and that is tolerant to any solvent used to wash away the supernatant. Gold-coated filters are very good for taking Raman and IR spectra of particles because they reflect the light and enhance the signal. IR reflectance spectra of particles on a gold-coated filter require no extra sample preparation or moving, and spectra of microparticles on gold typically have excellent signal-to-noise. In addition, attenuated total reflectance (ATR) spectra can be taken of the particles if the reflectance spectra are not very good or are significantly different from the library spectra, making spectral identification difficult. LIB spectra can also be taken on gold filters for particles that are about 10 µm.

It is important to consider what analytical technique would be appropriate for identification. LIBS analysis can provide detailed elemental composition of glass and metals and is therefore very helpful in finding specific sources. For example, glass flakes can come from vial delamination, whereas fibers can come from insulation around the plant, or lamination belts used, for example, to make transdermal patches. The presence or absence of elements in glass, including Ba, Ca, K, and Na, can be used to help identify the source. LIBS can identify metal composition as iron, aluminum, copper, or steel and therefore, the source from the processing or cleaning equipment, or from the plant environment can be determined. LIBS spectra of particles can be compared to samples of possible sources for better identification of the specific source. Steps that are taken to avoid the problems in the future would depend on the source. If it is the plant environment, then areas can be cleaned better or the process equipment can be isolated in clean areas. If it is the equipment itself, steps can include preventive maintenance of

TABLE 1

	Total Number	Size Distribution [µm]				
All Particles		≥2<5	≥5<10	≥10<25	≥25<50	≥50
1st 10-mL portion	5270	3993	1003	238	34	2
2nd 10-mL portion	3113	2459	550	91	12	1

Materials counted with the Single Particle Explorer (SPE)

FIGURE 4

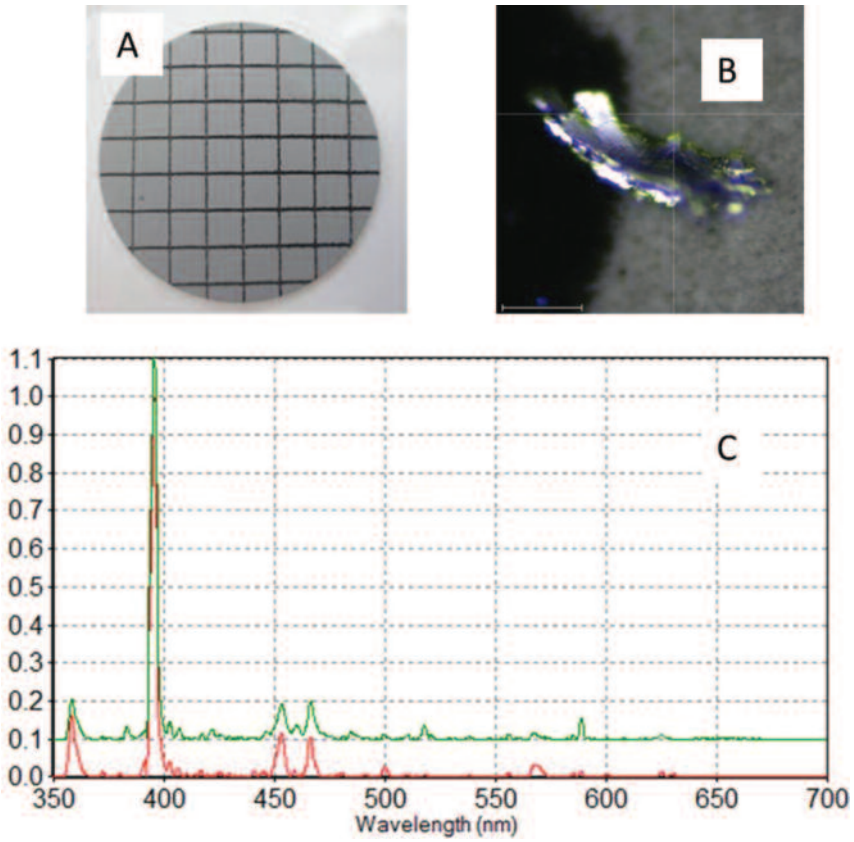


Image of a 47-mm diameter collodion filter (with a black grid) used for collecting particles. B) Image of the particle on the collodion filter. The black is the filter grid. C) The LIB spectra are from the particle (bottom, red spectrum) and the library match of aluminum (top, green spectrum).

more frequently replacing parts that wear, or specifying better quality parts. If the source is processing equipment, product-equipment interactions could be the source, and processing parts that will not interact with the product can be selected.

Which Analytical Technique to Use

It is important to know the advantages and limitations of analytical techniques so that the right ones can be used in the right order, and the data will not be misinterpreted. Raman is especially sensitive to chemical bonds with large electron clouds, while IR is sensitive to materials with strong dipoles, thus Raman and IR of the same sample can detect different functional groups to different degrees. For example, Raman can detect cellulose, but in a blue cellulose fiber, the blue dye with aromatic functional groups may give a much stronger spectrum, and the cellulose may not be easily detected. IR has much greater sensitivity to the OH groups in the cellulose, and less sensitivity to the dye with weak dipoles. So for a blue fiber, the cellulose bands dominate the IR spectrum (Figure 5).

Raman can be used to complement the LIBS elemental data because it can identify inorganic complexes and then help determine whether the elements are from pure metals or complexes.[8] LIBS spectra destroy about a 10-µm area of a particle, so it would be better to use a non-destructive technique first.

LIBRARIES

Hit Quality Index

Spectra are taken of unknown materials and then typically compared to library spectra for classification and identification of the chemical functional groups present, and where possible, specific identification of the unknown. "Spectral searching is intended as a screening method to assist the analyst, and is not an absolute identification technique, and hence, not intended to replace an expert in infrared spectroscopy and should not be used without suitable training."[9] Spectral searching is done by spectral matching algorithms, which are chosen based on the quality of the spectrum, including noise and baseline, as well as whether an exact match or just chemical identification are needed. Many algorithms work well and can include absolute value, correlation, Euclidean distance, first derivative, and least squares. The result of spectra searching is usually a numerical "match value" or "hit quality index (HQI)." These are numbers derived from a mathematical comparison of two spectra.[10] These values are not measures of the material purity, but are simply measures of correlation between the library reference spectra and the unknown spectrum.[10] Thus, these values often have less meaning than is commonly attributed to them. Correlation techniques do not provide any information about the probability that the match is valid, are highly dependent on the library content, including mis-named spectra and spectra of contaminated samples, and misidentification can occur between similar materials.[11]

The best libraries are made with specific known materials from the plant and process that are taken with the same instrument, the same techniques of sample presentation to the instrument, and the same methods of analysis that will be used for unknown material analyses.[10]

CONCLUSIONS

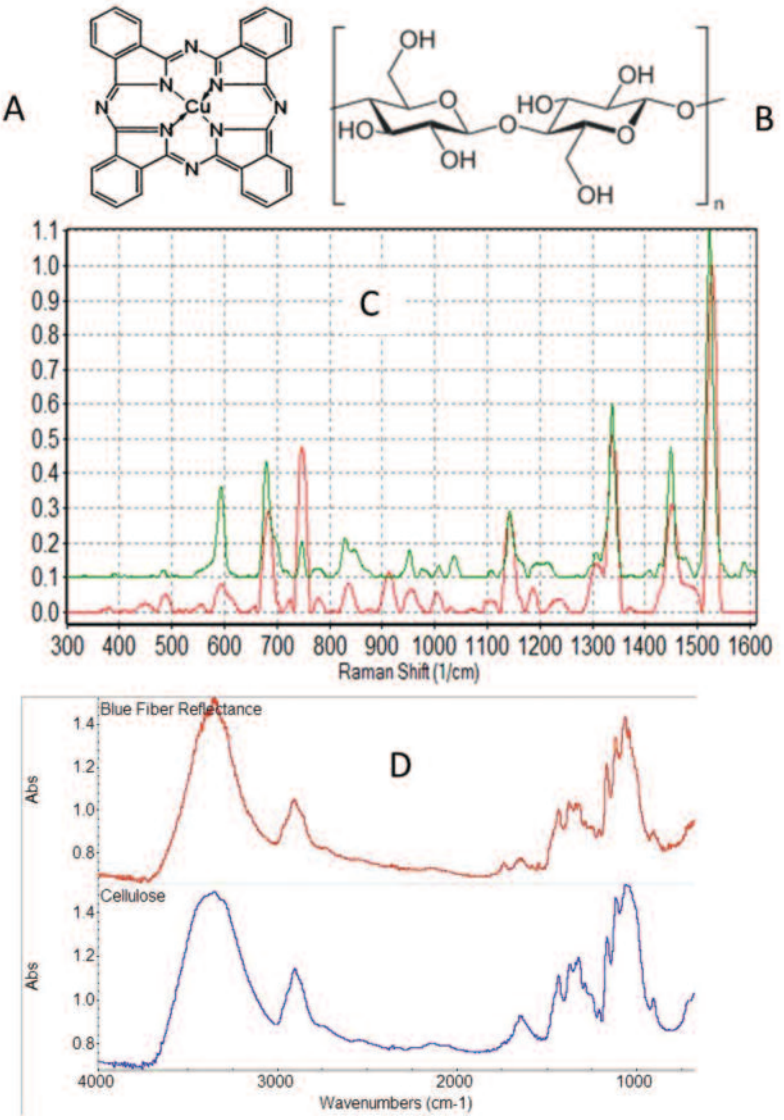
Particles from vials, syringes, stoppers, plungers, IV bags, process equipment, and filters were counted and identified. This provided information about sources, including wipes, personal protective equipment, glass, and general contamination due to unclean environment. Once the sources are determined, methods can be instituted to prevent contamination, improving product quality.

In order to implement proper analysis, it is important to understand the qualities of the method. For example, in situ analysis of particles in liquids can be complicated by bubbles and surrounding materials. Filtering samples onto appropriate substrates, such as gold-coated filters, was shown to be an excellent method for both counting and identifying particles and was an appropriate substrate for Raman, IR, and LIBS identification. Filtering avoids difficult and time-consuming manual particle isolation.

Understanding which spectroscopic identification technique to use is very important. Often, more than one technique is needed for accurate results. LIBS was shown to be useful for glass and metal identification, Raman was shown to be useful for organics and dyes, and IR was shown to be useful for material with strong dipoles. It was also shown that two techniques provided complementary information that gave more accurate identification.

Because libraries are essential for spectroscopic identification, it is important to understand that the HQI often has less meaning than expected and is highly dependent on library content and quality, as well as the method of analysis. Library quality is best if developed on the same instrument with the same analysis method. The advantages and disadvantages of different analysis methods relative to small particle identification were discussed. ◆

FIGURE 5



A) Molecular structure of Heliogen Blue. B) Molecular structure of cellulose. C) Raman spectrum of the fiber (bottom, red spectrum) and Heliogen Blue dye (top, green spectrum). D) IR spectra of the fiber (top, red spectrum) and library spectrum of cellulose (bottom, blue spectrum).

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BIOGRAPHIES

Dr. Kathryn A. Lee is the Lab Head for rap.ID Inc. with experience in pharmaceutical, consumer product, and chemical companies; establishing cGMP-compliant innovative spectroscopic techniques for quality improvement for products and processes. She has held several leadership positions in the Society for Applied Spectroscopy, developed an international course, Practical Problem-Solving in Chemical Analysis, and earned her PhD in Organic Chemistry.

Dr. Markus Lankers is President and Co-founder of rap-ID Particle Systems GmbH that develops and manufactures instruments for rapid particle identification and siliconization measurements. He researches and develops solutions for particulate analysis. He previously worked with Schering AG. He helped to establish the Visual Inspection of Parenterals Interest Group and serves as program co-chair for conferences on Visual Inspection of Parenterals in Europe and USA. He earned his PhD from Würzburg University.

Dr. Oliver Valet is Vice President and Co-founder of rap.ID Particle Systems GmbH, responsible for product development. He has more than 15 years of experience in industrial chemical analysis of particles. As an active member of the Respiratory Drug Delivery, the Royal Chemical Society, Parenteral Drug Association, American Association of Pharmaceutical Scientists, and the Apotekerverband, he has published his work continuously and presented in various conferences. He earned his PhD in Physical Chemistry from Freie Universität Berlin.

ORALLY DISINTEGRATING TABLETS

Designed With Patients in Mind: The Art of Patient-Centric Drug Formulation

By: Anthony Recupero, PhD

INTRODUCTION

Patient-centric formulations and dosage forms can benefit a range of target patient populations. They may also improve the market value of a pharmaceutical product, especially when drug formulation technologies are considered throughout the drug development process. Drug delivery technologies can be used to meet the needs of certain patient populations, such as pediatric, geriatric, and dysphagic patients; adolescents; and patients with neurological disorders, thereby encouraging adherence while supporting optimal disease management and improved outcomes.

Certain patient populations, including geriatric and pediatric patients, and patients who suffer from neurological disorders, often have difficulties swallowing tablet or capsule dosage forms. Dysphagia is seen in elderly populations with up to 22% prevalence in those aged over 50 years in the community setting—with even higher prevalence in assisted living facilities and nursing homes.[1] With pediatric patients, there is often a fear of choking when swallowing a solid oral dosage form, whereas the practice of "cheeking" (hiding medications in one's cheeks to avoid swallowing) often occurs in institutionalized psychiatric patients.

Patient-centric dosage forms, such as orally disintegrating tablets (ODTs), offer easier administration for patients who experience nausea or vomiting, and those with difficulty swallowing, including elderly and pediatric patients, people who have had a stroke, and patients who are bedridden. ODTs combine the advantages of an easy-to-swallow dosage form, such as a liquid, with the administration convenience of a tablet for increased adherence, particularly for pediatric and geriatric patients, and can address cheeking issues among psychiatric patients.

ODTs demonstrate a strong trend in the pharmaceutical industry, and the demand for ODTs is projected to reach $3.6 billion by 2020.[2] Preferred by patients over traditional dosage forms, ODTs are designed to disintegrate rapidly on the tongue. Disintegration should result in an easy-to-swallow, smooth suspension and, ideally, contain taste-masked drug microparticles to eliminate bitter drug aftertaste. According to the US FDA Guidance for Industry Orally Disintegrating Tablets, ODTs should disintegrate within approximately 30 seconds or less with no need for chewing or drinking liquids, meaning ODTs should be able to be administered by the patient with or without water.[3]

Geriatric patients face additional administration burdens because of the need to take multiple drugs, multiple times throughout the day. Dosage form design has helped address needs of elderly patients through variations of size, color, and shape, whereas long-acting formulations or combination products can assist in reducing pill burden.

By making drugs more palatable, taste-masking can improve compliance and extend product reach to patients who

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are more taste sensitive, such as pediatric patients. In the pediatric market (which is forecasted to be the fastest growing global drug market over the next 10 years) drug adherence can be challenging due to bitter-tasting medication.[4]

Patient nonadherence to medication results in an annual revenue loss of approximately $564 billion for the global pharmaceutical industry—in fact, this is a conservative estimate.[5] Factors such as unpleasant taste, inconvenience, and difficulty in administration, coupled with determinants of taste preference, such as genes, gender, and cultural and regional differences, are driving pharmaceutical companies to seek partnerships with drug delivery companies that have a proven track record in meeting patients' unmet medical needs.

Table 1 demonstrates how patient needs can be addressed by specific dosage forms. By addressing specific unmet patient needs, a unique formulation with a novel technology can add market value and differentiate the product, especially if it competes in a crowded therapeutic area. Market exclusivity can be protected by technology and product patents, potentially minimizing generic intrusion. An expert drug development partner with a broad range of proprietary technologies and experience in developing complex drug formulations, can optimize R&D returns by reformulating existing products or creating entirely new products.

TABLE 1

Specialized patient needs

Optimal patient dosing needs	Expected levels of importance for specific patient groups			
	Elderly	Pediatric	Dysphagic	Neurological disorders
Ease of swallowing (solid forms, quick dissolving tablets, granules, powders, etc)	++++	++++	++++	++++ (dose cheeking)
Reduced pill burden	++++	++	++	++
Convenient dosage form (ie, oral preferred vs intravenous or subcutaneous injection)	++	++++	+	+
Pleasant taste	++	++++	+	+
Identification, mix-up prevention (ie, optimized size, shape, and color)	++++	++	+	++

Table key
++++ = Extremely important
+++ = Very important
++ = Important
+ = Somewhat important

COMMERCIAL SUCCESS OF PATIENT-CENTRIC FORMULATIONS

The World Health Organization (WHO) estimates that there are approximately 3.2 million children worldwide living with HIV.[6] VIREAD® (tenofovir disoproxil fumarate) was originally approved by the FDA in 2001 as a once-daily 300 mg tablet for individuals aged 18 years and above for the treatment of HIV-1 infection in combination with other antiretroviral agents. In March 2010, the 300 mg dose was approved for use in the United States for adolescents aged 12 to 17 years, and in January 2012, three lower-strength, once-daily tablets of VIREAD in doses of 150 mg, 200 mg, and 250 mg were approved for children aged 6 to 12 years.[7] In order to provide a pediatric-optimized dosage form, the drug needed to be reformulated. Gilead Sciences, Inc., partnered with Adare to develop a pediatric oral powder formulation of VIREAD.[8]

By using Microcaps® Taste Masking Technology, Adare delivered VIREAD oral powder. Microcaps technology provides complete and uniform polymeric membranes of adjustable thickness, thereby effectively taste-masking drug particles.

Study results have shown that VIREAD oral powder achieved clinical bioequivalence compared with the original VIREAD tablet formulation.[8]

To help encourage accurate dosing, VIREAD oral powder features a multidose bottle with a calibrated measuring scoop. The use of Microcaps technology provided effective taste-masking of the active pharmaceutical ingredient (API).[8] VIREAD oral powder has been approved by the FDA and the European Commission.[8-10,*]

Another example of patient-centric formulation success was the development of an ODT formulation of a central nervous system (CNS) drug, which was co-developed by Adare with a private partner. Estimates are that this CNS condition affects 0.6% to 1% of the US

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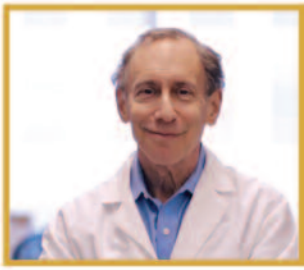

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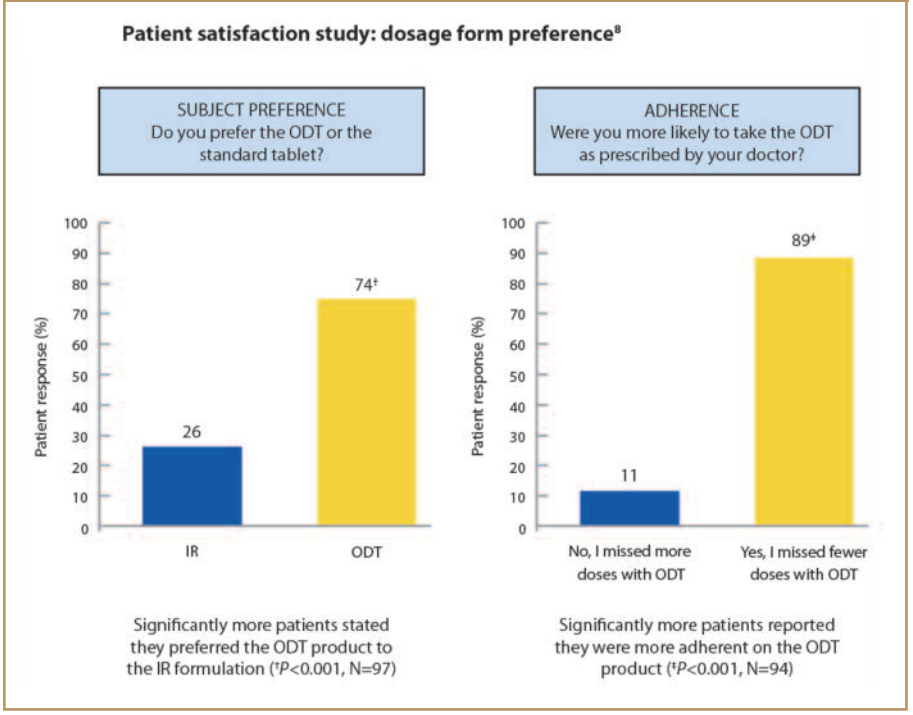

population, with the highest incidences in young children and the elderly.[11] The condition has a nonadherence rate of 30% to 50%. These patients may also have low self-management skills, require caregiver support, and have a high prevalence of depression as a co-morbidity.[12]

Another significant CNS condition has been shown to affect approximately 5.7 million adults in the US in a given year.[13] Furthermore, the National Center for Health Statistics reported that within a 10-year period, the diagnosis of this CNS disorder among adults had almost doubled. In the same time period, the number of diagnoses of this CNS disorder increased by 40 times in children and adolescents.[14] As in many chronic disease states with intermittent symptoms, medication nonadherence is a common occurrence and is associated with poorer outcomes.[15]

Adare was approached by its partner to consider patient-centric needs for the brand. The solution would be the development of a taste-masked ODT. In just 18 months, Adare developed an ODT form of the drug—from formulation, to successful pharmacokinetic (PK) testing, and completion of a new drug application filing with the FDA.

This dosage form was bioequivalent to the existing doses, and met the following criteria:

- An immediate release (IR) ODT with dose-proportional formulations to enable clinicians to titrate the medication
- Disintegration within 30 seconds, with rapid and complete release in the stomach
- Delivery of a taste-masked ODT with excellent organoleptic properties for patient acceptance, including taste, mouth feel, and swallowability

Using Microcaps technology, the API crystals were microencapsulated. The taste-masking process was combined with AdvaTab® Orally Disintegrating Tablets—providing the added benefit of rapid disintegration in the mouth without the need to administer with water.

ODT PATIENT SATISFACTION STUDY

Patient convenience and satisfaction with the AdvaTab ODT formulation was measured in a study of 97 patients who had been taking the IR formulation.[8]

Patients found the AdvaTab ODT to be significantly more convenient than the IR reference product ($P<0.001$) (see Figure 1), with convenience being defined as ease of use, ease of planning when to use, and convenient to take as instructed. Significantly more patients reported that they were more adherent with the AdvaTab ODT than the IR reference product. Overall, both patients and caregivers significantly preferred the AdvaTab ODT over the IR product.[8]

TECHNOLOGY OVERVIEW

Taste may be the most important organoleptic property for the acceptance of oral drugs, and many drugs require taste-masking. As such, many methods have been developed, with varying levels of success. Methods for taste-masking include sugar or flavoring additions and more sophisticated methods involving wax coatings, heat treatments, chemical modifications, and sensory blocking, such as with Microcaps technology.

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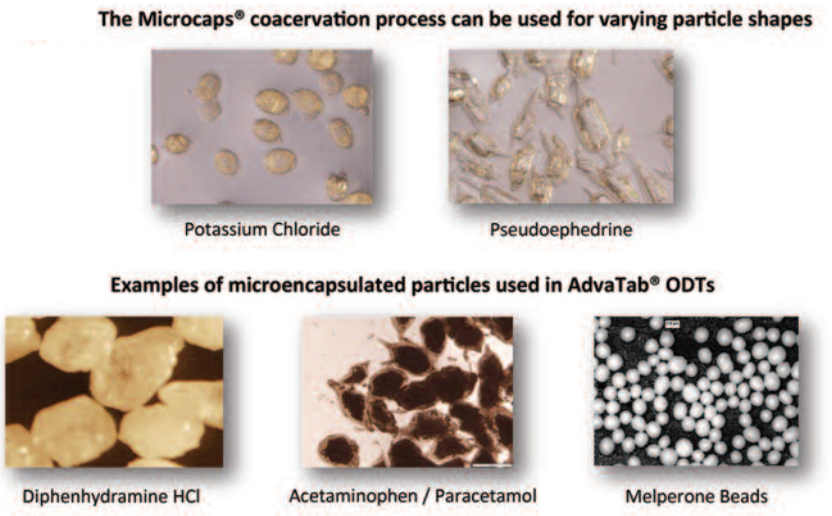
FIGURE 2



Microcaps technology achieves a uniform and efficient drug particle (crystal, granulate, or liquid) coating and may enhance overall patient adherence by improving the product's acceptability. Microencapsulation technology employs versatile and precise coating techniques to encapsulate individual drug particles. This process uses coacervation (ie, phase separation) and can also incorporate a spray-coating process, creating polymeric membranes of varying degrees of porosity and thickness to completely encapsulate drug particles. The membrane improves taste by forming a barrier between the drug and taste buds in the mouth.

The taste-masking membrane may comprise at least one gastrosoluble organic, inorganic, or polymeric pore-former. The gastrosoluble pore-former of the taste-masking membrane, being insoluble at saliva pH, provides effective taste-masking when placed in the oral cavity; however, the pore-former rapidly dissolves upon entry into the stomach for rapid release of the drug from coated/taste-masked drug particles, thereby enhancing the probability of success in achieving bioequivalence to an IR reference listed drug (RLD).

In addition to taste-masking, Microcaps technology can be combined with customized release profiles and used for encapsulation of liquids for oral powder delivery. Microcaps technology can also be used to separate incompatible APIs in fixed dose combination products. Figure 2 shows examples of various microencapsulated drug particles.

This versatile multifunctional technology has been used alone and in combination with other technologies to create innovative patient-centric dosage forms. AdvaTab tablets incorporate coated drug particles that are uniformly dispersed in a low-moisture, rapidly disintegrating matrix. Each ODT is formulated to achieve an acceptable taste, a disintegration time of approximately 30 seconds or less, and desired release profile. Additionally, AdvaTab tablets enable rapid disintegration in the mouth without water. AdvaTab tablets have been formulated to be bioequivalent to IR RLDs.

The technology features robust tablets that are suitable for multiple packaging configurations, including push-through blister packs (Figure 3) and high drug-loading capability—up to 500 mg.

SUMMARY

Patient-centric drug delivery enables the development of customized products across multiple patient populations, enhancing disease management through improved patient adherence. By partnering with an expert in drug delivery technology, whose portfolio features a broad range of proprietary technologies, pharmaceutical companies have the potential to add further value to their products and extend market exclusivity.◆

This article is intended to promote the proprietary technologies of Adare Pharmaceuticals. It is not intended to promote any product.

DISCLAIMER

VIREAD® is marketed by Gilead Sciences, Inc. Please see full Prescribing Information, including Boxed Warning, available at www.gilead.com.

FIGURE 3

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BIOGRAPHY

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SOFTGEL FORMULATIONS

Lipid-Based Drug Delivery System to Bring Poorly Soluble Drugs to Market

By: Ronak Savla, PhD, PharmD, and Jeffrey E. Browne, PhD

Gone are the days when creating a new oral drug dosage form was simply a case of mixing the active pharmaceutical ingredient (API) with a suitable excipient and manufacturing. The number of drugs in the development pipeline for which this is likely to be a successful strategy is limited. A growing number of investigational molecules have poor solubility, poor permeability, or both, rendering a simple tablet or powder in a capsule suboptimal in terms of delivering the drug to the patient in a predictable, reproducible, and effective fashion. This is a particular issue with many of the modern targeted cancer medicines. For example, tyrosine kinase inhibitors, while often given orally, frequently exhibit a significant food effect that can greatly impact their absorption.[1]

The Biopharmaceutics Classification System (BCS) can be used to categorize APIs according to their dose, solubility, and permeability. Those APIs amenable to simple tableting or powder in a capsule are likely to fall into Class I: molecules that are both soluble at their administered dose and permeable, whereas those that are neither soluble at a given dose nor permeable fall into Class IV. A large number of modern drugs – including most tyrosine kinase inhibitors – fall into Class II, having low solubility at the given dose but high permeability. Drugs that have poor permeability properties but readily dissolve represent BCS Class III compounds.

While this system represents a good way of identifying those compounds that may be good candidates for biowaivers based on *in vitro* dissolution data and serves as an aid for regulators in this regard, the system is not particularly useful for formulators and determination of suitable formulation approaches based on the properties of the compound. Specifically, it does not give sufficient insight into the solubility behavior of molecules in BCS Class II, where so many problematic compounds lie. Yet about two-thirds of compounds in the current development pipeline fall into Class II, with the likelihood of poor bioavailability, variable pharmacokinetics, and the distinct possibility of significant food effects. This not only puts patients at additional risk of developing toxicity-related side-effects, but leads to complicated dosing regimens and patient compliance issues.

As a result, a Developability Classification System (DCS) has been created.[2] This splits BCS Class II into two sub-classifications, providing an additional level of insight into a molecule's solubility properties. The aim of the DCS is to direct thinking toward the right formulation strategy more quickly by facilitating the selection of technology in a rational way.

DCS Class IIa represents those drugs where absorption is limited by the dissolution rate, while for those in Class IIb, the absorption is limited by the drug's intrinsic solubility. The DCS incorporates the concept of a solubility-limited absorbable dose, or SLAD, which represents the dose above which absorption of a compound is limited by its solubility. Above the SLAD, simply reducing the particle size to speed up dissolution is unlikely to be successful in improving the compound's exposure.

Particle size reduction, solid amorphous dispersions, and lipid-based formulations represent approaches to address the problems posed by Class II compounds, depending on whether the compounds are dissolution-rate limited or solubility limited.[3]

Particle size is commonly reduced using milling, micronization, or co-micronization techniques, and can be appropriate for Class IIa, where dissolution rate is at the root of the problem.

For Class IIb, where intrinsic solubility is the issue, successful strategies are likely to involve presenting the drug to the gastrointestinal system in a form in which it has already been solubilized. A solid dispersion technique such as hot melt extrusion can achieve this, as can formulation in a lipid-based drug delivery system (LBDDS).

A proper screening strategy is essential if the best formulation approach is to be selected at the outset. A number of in silico prediction tools are available that can steer the formulator toward one technology or another, but there remains no substitute for laboratory screening experiments. If these are carried out at an early stage, in a parallel fashion, rather than taking a "fit-for-purpose" approach when the project enters Phase II trials, the potential to accelerate development is significant. Efficacy and safety concerns can also be addressed at the outset.

Lipid-based systems are a proven technology for enhancing bioavailability, and the mechanisms via which lipid formulations enhance bioavailability have been comprehensively studied.[4,5] Difficult Class IIa and IIb compounds can often be formulated into effective oral dosage forms using lipid-filled soft capsules and are in widespread use being manufactured on a commercial scale for both medicines and consumer health products.

Once it has been established that a lipid-based strategy is likely to be successful, the next step is to determine which excipients or combination of excipients are best suited for a robust lipid-based formulation containing the compound that will result in enhanced bioavailability based on *in vitro* data generated. The lipid formulation classification system (LFCS) was proposed in 2006, initially classifying lipid-based formulations into four different categories (Type I – IIIB), with a fifth category (Type IV), being added a year later (Table 1).[4,5] The formulations are assigned to a category based on the types and amounts of excipients, and predicted behavior (characteristics) *in vivo*. Type I lipid formulations are pure oils and require digestion whereas Type IV lipid formulation do not contain oils and rapidly disperse into micelles.

It is possible for an expert in formulation to speed the path to market further by incorporating the principles of Quality by Design (QbD) at the preformulation stage, ensuring that the critical formulation and process parameters determined in laboratory studies are addressed adequately during product development. Examples of the parameters that might be included in the QbD process at the preformulation stage are: screening for solubility in excipients, biorelevant media, and lipid digestion products; excipient compatibility; API degradation; and the risk of precipitation upon dispersion and digestion.

Soft capsules are the ideal platform for delivering lipid-based systems for a number of reasons. First, most lipid-based formulations are either liquids, or semi-solids that have low melting points and are not amenable to development as solid dose forms. Also, the shell, or gel mass, is compatible with a wide range of lipid excipients, regardless of whether they are very lipophilic, hydrophilic, or even amphiphilic. If formulated correctly, the shell has little effect on the lipid fill and its intended performance properties *in vivo*. The lack of headspace and hermetic seal provides protection against atmospheric oxygen that may lead to degradation of APIs sensitive to oxidation. Properly designed shells rupture rapidly and then dissolve quickly in the gastrointestinal fluid, releasing the API in the lipid fill formulation and ensuring it remains solubilized throughout.

The vast experience gained over the years in the formulation of lipid-based systems and the selection of a suitable shell, or gel mass, has demonstrated the versatility of the technology to meet a

TABLE 1

	Characteristics	Excipients in Formulation Content of Formulation (%w/w)			
		Oils: triglycerides or mixed mono and diglycerides	Water-insoluble surfactants (HLB < 12)	Water-soluble surfactants (HLB > 12)	Hydrophilic cosolvents (eg, PEG, proylene glycol, transcutol)
Type I	-Pure oils -Limited or no dispersion -Digestion required	100	-	-	-
Type II	-SEDDS -Moderate dispersion needed to form an emulsion -Likely to require digestion	40-80	20-60	-	-
Type IIIA	-SMEDDS -Rapid dispersion to form micro- or nano-emulsion -May need digestion	40-80	-	20-40	0-40
Type IIIB	-SMEDDS -Rapid dispersion to form micro- or nano-emulsion -Digestion likely not needed	<20	-	20-50	20-50
Type IV	-Oil free -Rapid dispersion results in micellar solution -No digestion needed	-	0-20	30-80	0-50

Lipid formulation classification system[4,5]

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TABLE 2

Drug	DCS/ LFCS	Excipients	*F* (%)	PK Variability (CV%)	Food Effect
Enzalutamide	Class IIb/Type III	Caprylocaproyl macrogolglycerides (CCMG), butylated hydroxyanisole, butylated hydroxytoluene, sorbitol sorbitan solution	84%	Inter-subject ≤30 %	Can be taken with or without food

Profile of enzalutamide[12,13,15,16]

range of target product profiles with multiple product attributes. For example, the immediate release of a lipid-based fill that is engineered to spontaneously disperse, forming a very fine, thermodynamically stable emulsion can potentially improve absorption and reduce patient variability.

More recently, plant-based soft capsules have been developed containing polysaccharides in place of gelatin in the shell. These have found application both in the vegetarian, animal-free dietary supplements market, and the pharmaceuticals arena. Because the shell material is stable at higher temperatures than conventional gelatin-based shells, semi-solids and highly viscous liquids can now be heated so they are flowable on encapsulation machines and capable of being hot filled into soft capsules. As a result, fills that form semi-solid matrices at room temperature can be encapsulated in soft capsules and utilized to provide controlled release delivery of APIs.[6] It should be noted that film coated soft capsules have also been successfully employed as a means of controlling or targeting the release of APIs with a number of examples cited in the literature.[7-9]

The case of enzalutamide represents a good example of how a lipid-based system can provide benefits over a solid dose form of the drug or the drug in suspension. Enzalutamide is a fully synthetic, non-steroidal antiandrogen agent, approved for the treatment of castration-resistant prostate cancer.[10]

An ongoing Phase II trial indicates that it may also have potential for treatment in triple-negative breast cancer.[11] According to the DCS, enzalutamide would be classified as a Class IIb compound, which means that its intrinsic solubility limits its absorption.

In early non-clinical phases, the drug exposure levels of enzalutamide were lower when dosed in a solid dose form or in a suspension compared to formulations wherein enzalutamide was in a fully dissolved state.[12] This supports enzalutamide being classified as a DCS Class IIb compound. In early studies, drug absorption was seen to be hindered by enzalutamide's slow dissolution rate.[12,13] This would appear to imply that enzalutamide is a DCS Class IIa compound, and particle size reduction technology could be employed. However, the SLAD of enzalutamide is 7.3 mg, and the administered dose is 160 mg. Therefore, particle size reduction alone is not likely to improve the dissolution rate for the required dose of enzalutamide to be fully absorbed, and another formulation approach should be considered given the compound is solubility-limited (DCS IIb). Based on its classification, DCS would suggest a lipid-based or solid dispersion formulation of enzalutamide would be the best formulation approach for enzalutamide. This proved to be the case as a lipid filled soft gelatin capsule was selected and developed as the market entry dosage for the product. The excipients of the commercial lipid-based fill formulation are shown in Table 2 and would be classified as a Type III lipid formulation according to the LFCS. Studies have also shown this commercial formulation has high bioavailability, low inter-subject pharmacokinetic variability, and a linear dose escalation from 30 mg to 600 mg.[12] From a patient perspective, no significant food effect was observed, and the dose can be taken without regard to food.[14]

There are many benefits in using LBDDSs when formulating poorly soluble and poorly permeable drugs, and soft capsules for their delivery. In addition to overcoming solubility and permeability issues, they are well understood, widely accepted by both patients and regulators, and have a long history of large-scale manufacture and commercial success.

Formulation screening, development, scale-up, and commercial manufacture of LBDDSs are all activities where considerable expertise is required. If this experience is not available in-house, which often is the case, then choosing an outsourcing partner with experience and a proven track record is critical. As a general rule, selecting a partner that is able to carry out the whole spectrum of activities from formulation development through to commercial manufacture makes sense as this simplifies and speeds up product development cycle times by eliminating the need for work at multiple partners/sites and removing tech

transfer steps required for ultimate commercialization of the product.

The costs of drug development have escalated greatly in recent years. The latest, 2016, estimate of the total cost of getting a new molecular entity to market, from the Tufts Center for the Study of Drug Development is $2.6 billion.[17] This reflects not only the growing demands of the regulators for ever more studies to prove safety, but also the increasing complexity of the product types being developed.

Lack of drug solubility and permeability are two significant contributing factors to the return on investment from new drug launches reaching historical lows.[18] However, today, it is possible to address compounds with difficult physicochemical properties and unfavorable absorption characteristics early on in the development process. By doing so during preclinical development, both costs and attrition rates can be reduced. ◆

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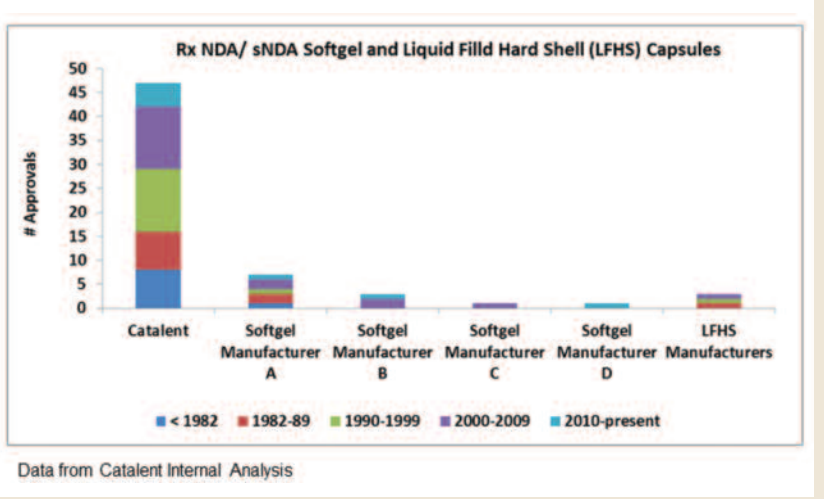
SIDEBAR



CURRENT MARKET LANDSCAPE FOR LIPID-BASED DRUG DELIVERY SYSTEMS

Lipid formulations have the longest commercial success track record among enabling technologies measured by the number of New Drug Applications (NDAs).[3] There are numerous benefits for using LBDDSs for poorly soluble and poorly permeable drugs, and the use of soft capsules as a delivery platform for their successful commercialization. A high-quality, reputable industry partner is desirable for the successful, efficient development, scale-up, and commercial manufacturing of soft capsules. It is particularly important to choose a partner that has the experience and knowledge to help design an optimal lipid formulation based on the specific physicochemical properties of the API during the preclinical stages. Additionally, it is advantageous to use the same partner that does the development for scale-up and commercial manufacturing because the process is considerably simplified when all activities needed for a successful product are performed within the same partner entity or network. Only a handful of contract development and manufacturing organizations are capable of taking a new compound from preclinical development through commercial-scale cGMP manufacturing. As of this time, only five soft capsule manufacturers have successfully navigated the approval of soft capsule NDAs or supplemental NDAs (sNDA). Of the five, only three manufacturers have successfully submitted and received approval of soft capsule NDAs. The table below illustrates the number of supported NDAs and sNDAs by company.

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BIOGRAPHIES

Dr. Ronak Savla is a Scientific Affairs Manager with Catalent Pharma Solutions and the Catalent Applied Drug Delivery Institute. He earned his PharmD and PhD from Rutgers University. His current research interests are in the application of in silico models and simulations to aid in drug formulation design, integration of novel formulation technologies into the industry, and patient-centric research. He was awarded the American Society of Health-System Pharmacists Foundation Student Research Award for his research project during pharmacy school. Dr. Savla is author and co-author of over 35 publications including peer-reviewed papers, magazine articles, conference proceedings, and posters.

Dr. Jeff Browne began his career with Catalent in 1994, and since then he has held a number of positions, before becoming R&D Director and US Platform Leader of Pharma Softgels.These included Executive Director & Division Head of Pharmaceutical Development in Research Triangle Park, NC, and most recently, Technical Director, Pharmaceutical Softgels. He is an active member of the American Association of Pharmaceutical Scientists (AAPS), and has served on several of their Focus Group committees. He is a frequent presenter at both regional and national AAPS meetings. Dr. Browne earned his PhD from Purdue University in Industrial and Physical Pharmacy.

COMPUTATIONAL METHODS

Formulation Development: An Innovative, Simulation-Based Approach

By: Tom Reynolds, PhD, Matt Wessel, PhD, Sanjay Konagurthu, PhD, and Marshall Crew, PhD

INTRODUCTION

We know the cost of developing a prescription drug is estimated at $2.6 billion, and takes 10 to 15 years from target selection to drug approval with an overall success rate around 10%.[1,2] Furthermore, only about 35% of drug discovery projects succeed in delivering experimental drugs ready for clinical testing.[3] In order to improve productivity, companies have been leveraging computational chemistry to screen and identify potential drug candidates at the earliest stages of drug discovery. These methods are a viable approach to shortening development timelines and achieving better success.

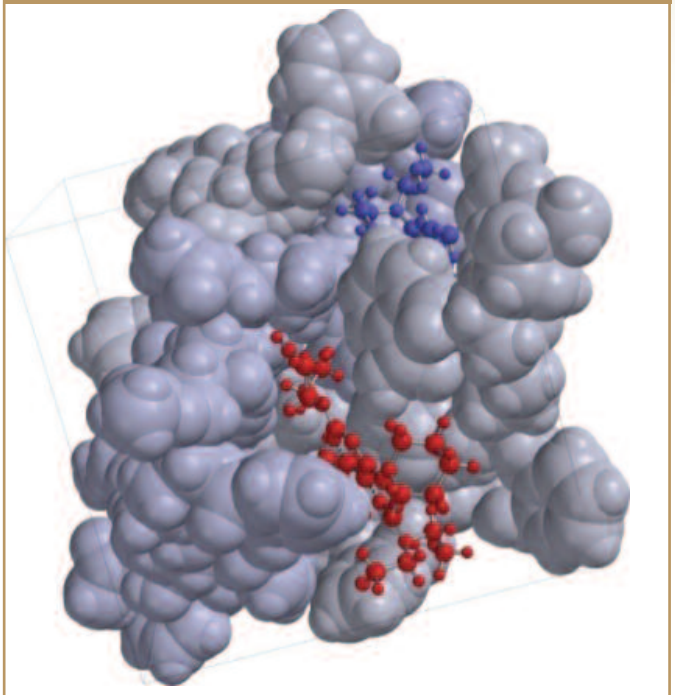
Throughout the past decade, the speed and performance of computational modeling methods using quantum mechanics (QM) and molecular dynamics (MD) has significantly improved allowing for rapid in silico screening of drugs in more complex environments. To further improve success rates and reduce development time and cost, early consideration of the drug delivery method and formulation approaches should begin in parallel with drug discovery and development programs.

Throughout the past few years, Patheon has taken this approach a giant step forward, utilizing MD and QM simulations to support efficient and robust formulation development. As a pioneer of this approach, Patheon uses computer modeling simulations in the early phases of the development process to 1) rapidly identify candidate excipients for drugs, 2) predict key experimental properties of the formulations, and 3) determine drug loading and formulation stability.

A 2014 paper from Patheon's ORP division scientists discuss the use of predictive modeling in formulation development and directed product analyses to significantly reduce time to market and overall product costs. The paper states that to enable this approach in pharmaceutical formulation, there is a strong need for a deeper mechanistic understanding to support efficient formulation activities for poorly soluble molecules.

The approach enables formulators to efficiently select and

FIGURE 1



Molecular dynamics (MD) simulation of dipyridamole in the excipient polyvinyl acetate phthalate (PVAP). This reveals drug binding in pockets of the polymer; PVAP in Grey space filling, dipyridamole in Red and Blue ball and stick.

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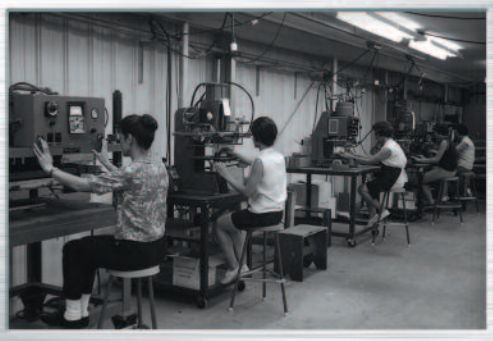

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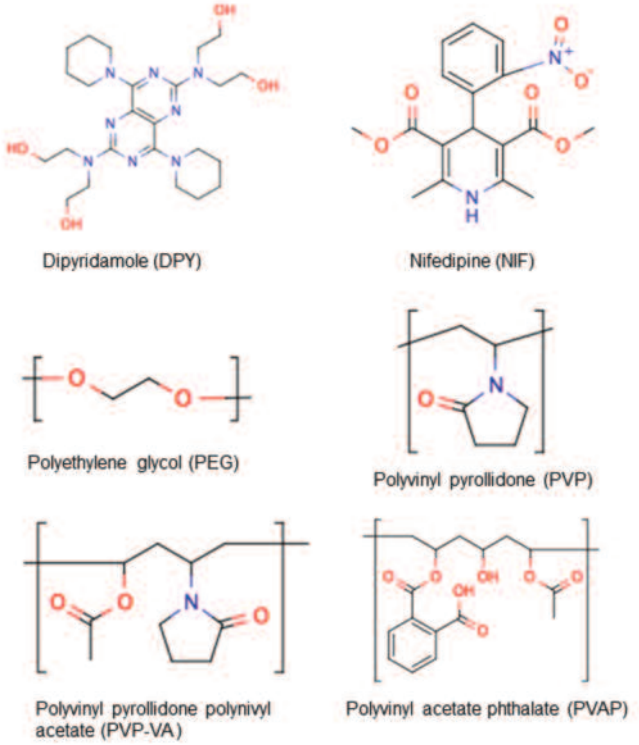
FIGURE 2



Representative structures of model drugs and polymers (excipients) evaluated in this study.

develop an optimum set of materials and methods for use in a solid dispersion, and inform why these choices are successful. The approach is especially valuable for BCS Class II and Class IV drugs, which can demand unique and challenging formulation methods.[4]

Selecting the optimal system for formulation development by traditional methods can take a vast amount of time in a laboratory and can be extremely costly. By understanding the simple chemical structure of a drug and candidate excipient(s), scientists can rapidly predict what might otherwise be measured in the laboratory. Broadly, the advantages of this approach are to significantly reduce costs and improve efficiency and accuracy prior to starting laboratory studies.

MD and QM simulations are a powerful tool for accomplishing the aforementioned. They provide insight into molecular-level behavior and interactions between drugs and excipients. Direct calculation and visualization of these interactions provide valuable insight into the formulation approach. For example, the glass transition temperature (Tg) of a drug-excipient mixture as a function of drug loading provides a strong indicator of the thermodynamic stability of the formulation. Infrared (IR) spectra can be used to identify the molecular level moieties involved in these interactions. Having a valid computational approach to predict the Tg and IR spectra of drug-excipient systems can be extremely insightful and reduce the amount of laboratory screening experiments required.

MD STUDIES OF THERMAL BEHAVIOR FOR AMORPHOUS BINARY DRUG AND EXCIPIENT SYSTEMS

Study Objective

Patheon conducted studies to evaluate in silico methods to characterize the thermal behavior and molecular-level interactions of pure drugs, excipients, and drug-excipient systems using MD and QM simulations.

The combined approaches provide the ability to observe and visualize molecular-level behavior and further predict relevant thermodynamic information, such as phase transitions

TABLE 1

Pure Component Glass Transition Temperature T_g °C (K)

Component	Calculated	Experimental
DPY	86 (359)	81 (354)
NIF	95* (368)	45 (318)
PVP	110 (383)	101 (374)
PVP-VA64	135 (408)	110 (384)
PVAP	95 (368)	120 (394)
PEG400	-38 (235)	-68 (205)

Predicted and experimental glass transitions temperatures (Tg) values for pure components.

TABLE 2

Drug-Polymer Dispersions Glass Transition Temperature T_g °C (K)

Drug wt%	Calculated	Experimental
25 DPY PVP	99 (372)	97 (370)
50 DPY PVP	85 (358)	82 (355)
25 DPY PVP-VA64	118 (391)	101 (374)
25 NIF PVP	137 (410)	117 (390)
25 NIF PVP-VA64	127 (400)	105 (378)

Predicted and experimental glass transitions temperatures (Tg) values for drug-polymer dispersions. Experimental measurements performed on spray- dried dispersions.

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(eg, glass transitions) and infrared spectra. These predicted values allow for the construction of models for application to new drug-excipient systems prior to embarking on time-consuming laboratory experiments.

Methods

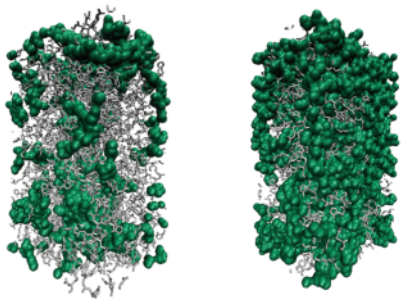
The structures of the drugs and polymers (excipients) evaluated in this study are shown in Figure 2.

MD simulations were performed on drug excipient mixtures with varying drug loadings.[5] Interactions between drug and polymer are readily visualized as a function of drug loading as shown in Figures 3 and 4. These figures provide an illustration of how increased drug loading leads to drug-drug interactions.

To calculate thermodynamic properties, such as Tg, the temperature of the simulations were started at 500K and cooled to 250K in 10K intervals. Cooling cycles were done using an NVT ensemble (constant volume), and equilibration was done using an NPT ensemble (constant pressure). The production run used to calculate density at each temperature was an NPT run of 500,000 steps, with a step size of 1 femtosecond. Molecular dynamics simulations were conducted on pure component and drug-polymer dispersion systems. By collecting density data at periodic temperature intervals, a breakpoint in the temperature/density plot is observed. It is at this point that the Tg can be inferred. A representative example for dipyridamole in PVP-VA64 is shown in Figure 5.

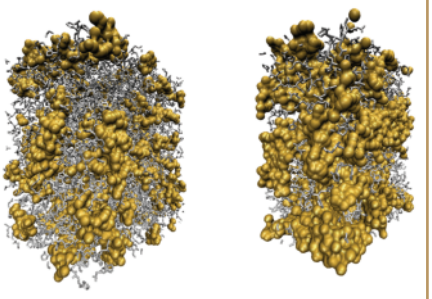
Tables 1 and 2 provide calculated and experimental data for an array of pure components and spray-dried drug-polymer dispersions. As can be seen, there is reasonable agreement between calculated and experimental data for the pure components. Differences between the glass transition temperatures of the pure components and the dispersions is a result of intermolecular interactions between the drug and polymer. These interactions can be inferred from infrared spectra.

FIGURE 3



Molecular dynamics simulations of dipyridamole/PVP-VA64 solid dispersions. Left: 25 wt% dipyridamole, Right: 50 wt% dipyridamole; T = 300 K, t = 0.5 ns. Green structures are dipyridamole, grey structures are PVP-VA64.

FIGURE 4

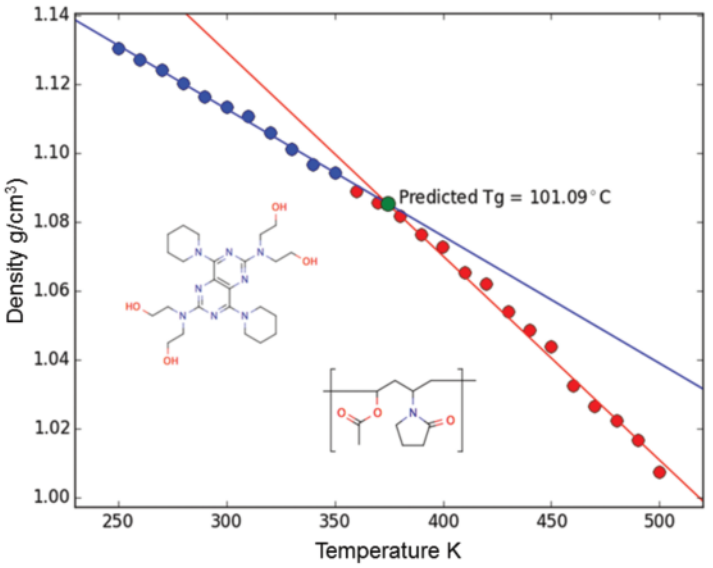


Molecular dynamics simulation of nifedipine/PVP-VA64 dispersions. Left: 25 wt% nifedipine, Right: 50 wt% nifedipine; T = 300 K, t = 0.5 ns. Gold structures are Nifedipine, grey structures are PVP-VA64.

To calculate the infrared spectra quantum mechanical calculations, density functional theory (DFT) was chosen (EDF2 with the 6-31g* basis set). Experimental Fourier Transform Infrared (FTIR) spectra were conducted on pure amorphous drug. Spray-dried dispersions of the pure polymer and drug polymer dispersions were prepared as a function of drug loading to provide the validation data for the MD and QM models.

Using the approaches described, we demonstrated the ability to predict and visualize the molecular-level interactions responsible for driving the thermodynamic behavior of drug-polymer systems. The approach can be extended to predict the behavior for new and unique drug-polymer systems.

FIGURE 5

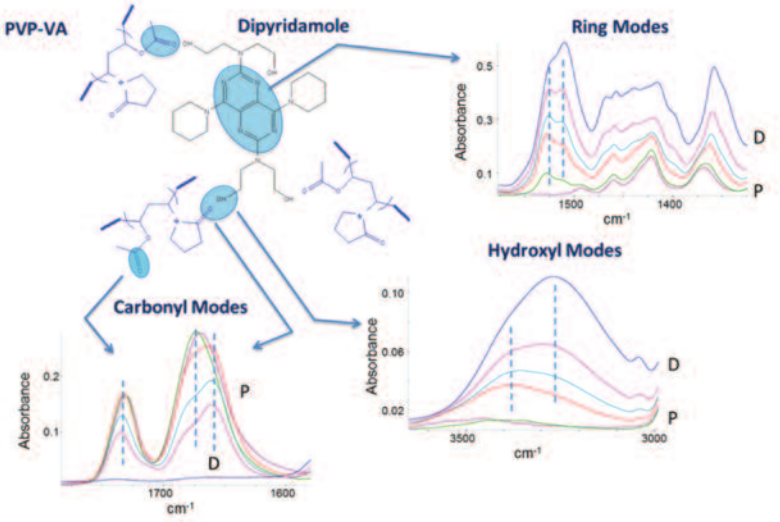


Derivation of predicted glass transition temperatures (Tg) for dipyridamole, PVP-VA64 and related dispersion systems.

LOOKING AHEAD

Computational methods such as QM and MD simulations are playing an ever-expanding role in drug discovery and development, and transforming advances in drug development at all stages. Consideration of drug formulation approaches at the very early stages of drug development promises to improve success rates and reduce development time and cost. Early consideration of the drug delivery method and formulation approaches should begin in parallel with drug discovery and development programs. QM and MD simulations provide key insights into the drug formulation process. With an increased understanding of drug-excipient interactions at the early stages of drug development, it becomes possible to select and design better molecules, reduce resources and costs, and

FIGURE 6



Infrared spectra of dipyridamole/PVP-VA64 dispersion as a function of drug loading. Vibrational modes in specific spectral regions are highlighted showing inter- and intra-molecular interactions; D=drug and P=polymer.

significantly improve the success rate in bringing a drug to market.◆

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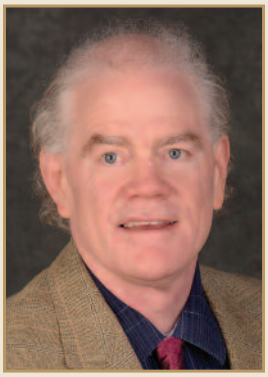
5. MD simulations were performed using Large-scale Atomic/Molecular Massively Parallel Simulator (LAMMPS) software with a customized force field and parameter set. The customization was extracted from the Optimized Potentials for Liquid Simulations (OPLS) force field.

BIOGRAPHIES



Dr. Tom Reynolds is Principal Scientist at Patheon, PDS Global Sciences, where he is responsible for development of a drug formulation and solubilization technology platform that provides formulation options using computational methods. He has over 20 years of experience in research, development, and management of programs in nanotechnology, crystal growth, formulation, and computer modeling. He earned his PhD in Chemistry from Oregon State University.

Dr. Matthew D. Wessel is Principal Scientist at Patheon, where he is responsible for developing predictive computational approaches for solving drug solubility and formulation problems. Prior to Patheon, he was a Solutions Architect at Schrödinger, worked for Bend Research, and was an associate research fellow at Pfizer. He earned his PhD in Chemistry from The Pennsylvania State University and his BS in Chemistry from Washington State University.

Dr. Sanjay Konagurthu is the Senior Director, PDS Global Science, for Patheon. He has over 18 years of experience managing the development of drug compounds from the discovery interface through clinical and commercial manufacturing. His expertise spans a broad spectrum of therapeutic areas involving formulation and process development of drug delivery platform technologies including solubility enhancement and modified release. Sanjay has performed and managed the formulation and process development for a broad range of NCEs and lifecycle management of marketed products. He earned his Bachelor of Technology degree from the Indian Institute of Technology (IIT), Madras (Chennai), and his PhD from the University of Colorado, Boulder, both in Chemical Engineering.

Dr. Marshall Crew became the VP, Global PDS Scientific Excellence at Patheon after Agere Pharmaceuticals (where he was the President, CEO & Founder) was acquired by Patheon in 2015. Dr. Crew has devoted his career to improving oral bioavailability, developing innovative technologies and approaches for the delivery of poorly soluble drugs and then managing their application to achieve client success. His scientific expertise includes formulation design and development, solid state characterization of drug substance and product, and computational modeling (predicting shelf-life and pharmacokinetic and bioavailability for oral, devices and parenteral delivery). He earned his PhD in Physical Chemistry from Oregon State University.

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Special Feature

Injectable Drug Delivery: Key Trends Define Device Design Now & in the Future

By: Cindy H. Dubin, Contributor

Gerresheimer's Gx RTF® ClearJect® features an integrated cannula made from COP to handle sensitive medications and high-viscosity agents.

The global injectable drug delivery devices market is expected to increase from around $11.6 billion in 2013 to around $ 17.5 billion in 2018.[1] Growth is being attributed to the rising prevalence of chronic diseases, the biologics market, technological advancements, and demand for self-injection devices, which are expected to experience the highest growth rate of 16.1%.

Biologics Driving Longer Syringes & Wearable Technology

With the growth of the biologics market, four of the world's top-five selling drugs are delivered by injection. Because these drugs are complex, biologics often require robust design efforts and present delivery challenges.

"There is a challenge with how to best deal with high-volume injections and highly viscous biologic drugs," says Terence O'Hagan, General Manager, Haselmeier, Inc.

Typically, in the biotech sector, the 1mL needle syringe is the most frequently used format for subcutaneous injections, explains Claudia Petersen, Global Director Business Development, Gerresheimer Bünde GmbH. "But the trend toward larger dosage volumes brings with it an increasing demand for 2.25mL needle syringes."

Additionally, with the emergence of biologics, wearable devices are in high demand," says Mark Hassett, Vice President, Sales and Business Development, Medipacs, Inc. "In fact, the market for devices to address these next-generation biologics requiring larger-volume injection capabilities is estimated to be $7-10 billion in the next 5 years."

Connected Technology Improves Compliance

In addition to wearable devices, experts see a trend towards connected devices. Here, a device is connected to a smartphone and tracks and reports injections to doctors and healthcare providers. The connected smartphone may remind the patient when to take the next injection, improving compliance, and if the patient forgets to inject, the caregiver could receive an alarm from the system.

"With a connected device, the smartphone becomes part of the injection experience," says Simon Michel, CEO of Ypsomed. "The screen may give the patient instructions about how to use the device, and in the event that the patient needs further support, a hotline may be called directly from the connected app."

According to Mr. Michel, initial connected devices will be smart reusable add-ons that will be used in combination with disposable devices. However, the technology will evolve to disposable devices. From a technological perspective, Mr. Michel says this presents some challenges:

- Connection between the device and smartphone must be established by Bluetooth or near-field communications (NFC). Bluetooth is too expensive to integrate in a disposable device and NFC doesn't have far enough reach.
- It is not feasible that a disposable device has its own electrical power. The power must come from the smartphone or another device.
- IT infrastructure needs to be built, and a cloud solution needs to be provided, to save and share the data.

"These challenges show that communication technology has to advance and that many more questions will need to be solved before disposable devices with integrated connectivity will be ready for the market," says Mr. Michel.

Self-Injection & a Human-Centric Focus

Until connected devices reach maturity, device developers will continue to seek more mainstream ways of enhancing the injection experience. Many are turning to Human Factors Engineering.

"Device designs have begun to shift towards a user-centric approach," says Bill Welch, Chief Technology Officer, Phillips-Medisize. "By applying Human Centered Design principles to the development

of injectables, we minimize these user-related risks and improve user adherence and persistence."

"Device innovations are driven by user preferences and human factors studies," agrees Sagarika Bose, PhD, Senior Manager, Technology Development, Terumo Pharmaceutical Solutions, Terumo Medical Corporation. "Subcutaneous injections are becoming the choice of pharmaceutical companies, device manufacturers, and patients due to the advantages of self-administration, ideal injection volume of 1mL, and use of fixed doses in prefilled syringes. These devices are focused on ease of use, patient comfort, compliance, and adherence. The devices should be compact, easy, reliable, tolerable, precise, and provide easy instructions and solutions for patients with limited dexterity and eye sight, and should cause less pain."

8 Qualities of Future Devices

No matter the type of injection device, Cambridge Consultants revealed eight qualities that injectors will have in the future:[2]

1. Universal: They will operate with any primary container without the need for a drug transfer step.

2. Customizable: Embedded electronic features will allow customization depending on the intended user type.

3. Upgradable: Connectivity capabilities will allow devices to be remotely upgraded, making the task of lifecycle management easier.

4. Green: Devices will further align with the increased requirement for greener technologies. Energy-harvesting technologies will replace batteries and make the end-of-life management of devices much easier and greener.

5. Empowering: Injectors will allow patients to take control of their disease state by monitoring their drug performance and recording relevant everyday activities. Access to real-time and historical data will empower patients who want the ability to better manage their disease state. Drug delivery devices will also be able to give feedback to patients and this information will be followed up with instructions on how to improve.

6. Intelligent: Delivery devices will be able to distinguish between the different types of drugs they deliver, how much they deliver, and when they deliver them. They will be used as authentication devices for drugs administered, providing extra control to the supply chain of drugs.

7. Likable: Drug delivery devices will adopt design features that resonate with patients and increasingly look more like consumer accessories.

8. Extended shelf life: Devices will have limited features that may limit their shelf life and constrain the manufacturing and supply processes of manufacturers.

Drug Development & Delivery magazine asked some leading device developers to describe their current injection technologies and explain how these devices are addressing the trends described above.

Bespak Europe Ltd.—New & Improved Autoinjectors Have Distinctive Features in the Market

Bespak works closely with biopharmaceutical partners to develop customized device designs that are suited to the needs of specific patient groups. Those designs reflect inputs from a range of key experts and stakeholders, including healthcare professionals and patients. Data generated in-house and by the company's biopharmaceutical partners' studies are also considered.

"As a result, with our new proprietary compact energy source VapourSoft™ technology, we are able

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Reference: 1. Bonds, R. S., Asawa, A., & Ghazi, A. I. (2015). Misuse of medical devices: a persistent problem in self-management of asthma and allergic disease. Annals of Allergy, Asthma & Immunology, 114(1), 74-76.e2. doi:10.1016/j.anai.2014.10.016

Bespak's Syrina™ S autoinjector is powered by the VapourSoft™ compact energy source.

to create some of the smallest and most unique device designs in the market today," says Steve Kaufman, Global Business Development Lead, Bespak Europe Ltd. "This gives our customers the flexibility to develop new devices with distinctive form factors and a significant advantage over traditional linear spring-based systems."

Bespak has refined its VapourSoft™ powered Syrina™ autoinjector range of devices. The Syrina S autoinjector design is now platform-ready and suitable for 1mL/2.25mL prefilled syringes. The Syrina AR autoinjector, featuring automatic insertion and automatic retraction, will be available toward the end of this year.

Bespak has focused on three specific features with these devices: customizable, empowering, and universal. "Different patient groups have different needs, for example, dexterity is a concern for a number of patient groups. Bespak has worked with customers to use special materials to enhance the "gripability" of devices and make it easier for patients to self-inject. Many of our new devices are also smaller than traditional systems, which can be impractical to carry. This empowers patients to lead a more "normal life" by being able to take their devices with them. These devices are also more discreet, by having a less medical look/feel."

Devices also need to accommodate the most common primary containers. Most of Bespak's devices are designed to allow for universal standards and ensure that if the body of the device needs to be changed for different patient groups, one device could easily be used for a number of different injectable products. Additionally, Mr. Kaufman says the VapourSoft range of devices addresses issues of injection volumes and higher viscosity liquids to allow self-administration.

Looking ahead, he says that partnerships will become increasingly important to ensure the need for injectable devices is met. By working with its sister company, Aesica, Bespak is beginning to support its customers with a complete offering from start to finish, as well as with drug-device combination products.

"Many biopharmaceutical companies are looking for device suppliers that are true partners in developing drug-device combination products. Aesica has the capability to manage CMO filling operations for our customers, which can be combined with our experience in the design, development, and manufacture of drug delivery devices in both low and high volumes. In addition, Aesica can provide final assembly, labeling, and packaging services for devices such as autoinjectors."

The Credence Companion Reconstitution Platform allows drug manufacturers to address their needs across the product life-cycle spectrum.

Credence MedSystems—A Platform of Reconstitution Safety Devices Satisfies Needs Across the Life-Cycle Spectrum

Injectable drug manufacturers face the challenge of addressing product, market, and user dynamics that place competing requirements on their products. The biologic injectables that fill their pipelines are often unstable as a prefilled solution and, therefore, require point-of-use reconstitution, explains John A. Merhige, Chief Commercial Officer, Credence MedSystems, Inc. "This is a cumbersome and time-consuming process that is ripe with opportunity for user error and/or accidental needlesticks. Yet, the drug manufacturers must still provide their end users an easy, straightforward, and safe experience to promote adherence."

Additionally, manufacturers must plan and manage the full life cycle of their products with the goals of getting to market fast, maximizing market share, and extending useful life. To address these competing demands, biopharma manufacturers need a platform of injection devices that provides suitable options at each stage along the life-cycle spectrum, while ensuring consistency in use, market differentiation, and compliance to needlestick safety and reuse prevention mandates, says Mr. Merhige.

The Credence Companion platform of reconstitution devices shares common themes across the products: the user completes the injection (marked by an end-of-dose click) and then the needle automatically retracts through the stoppers and into the plunger rod and syringe barrel, preventing the syringe from being reused. However, each product can play a different role in a manufacturer's strategy and a drug's life cycle.

The Luer Companion is the most straightforward to implement and most closely resembles conventional reconstitution as the user delivers the diluent into a drug vial and draws the reconstituted solution back into the syringe. Credence's needle retraction technology allows this mixing procedure to occur without any potential for premature activation of the safety mechanism. The added benefits of the Luer Companion include needle-connection security, end-of-dose cues, passive needlestick safety, reuse prevention, and component reduction. Additionally, because the drug manufacturer can choose from readily available syringe and elastomer primary package components, and because Credence components do not interface with the drug product during storage, the development and regulatory path to market is shortened and simplified, says Mr. Merhige.

Credence has extended the platform to include the Companion Dual Chamber Reconstitution Safety Syringe for drug manufacturers looking to enhance and simplify the user experience in a market where delivery of healthcare is moving to the home and injection of medication is increasingly performed by self-injectors. Consistent with Credence's *Innovation Without Change* design philosophy, the Companion Dual Chamber uses a standard uniform diameter glass barrel (syringe or cartridge), standard stoppers, and standard needle shields. When using the Companion Dual Chamber, the user presses on the plunger rod to mix the two components that had previously been separated; the diluent in the rear chamber passes into the front chamber through a newly formed channel in a standard stopper.

"By increasing the intuitiveness, efficiency, and ease of use, this solution promotes adherence to prescribed medication regimens, reduces the likelihood of user error and inaccurate dosing, and creates an enhanced drug-device combination product for the drug manufacturer," says Mr. Merhige. "The Companion Dual Chamber is a solution for drug products whose users range from novice self-injectors to time-pressured healthcare providers."

DALI Medical Devices—Auto-Needles Improve Patient Compliance & Adherence

DALI Medical Devices has developed a proprietary new line of safe, easy-to-use autoinjectors. "Innovative Safe Auto-Needles (SANs) address the unmet needs we identified in the growing injectable drug delivery arena," says David

Daily, MSc & MBA, CEO & Co-founder, DALI Medical Devices Ltd. "Literature has supported the assumption that autoinjectors and prefilled syringes are both viable options for self-injecting patients, each with its own set of advantages and disadvantages."

DALI has performed a market research study with patients and healthcare providers (HCPs) to uncover patients' preferences between autoinjectors and prefilled syringes. The survey was intended primarily for individuals experienced with self injection or caregivers and HCPs administering injections in three main applications: diabetes, Multiple Sclerosis (MS), and Rheumatoid Arthritis (RA).

The study results showed that a significant percentage of patients prefer to control injection speed and benefit from the ease of use of autoinjectors. A drug delivery device that combines the ease of use of an autoinjector with the pain level similar to prefilled syringes (by manual control of the medication injection speed) would be advantageous, explains Mr. Daily.

"Our conclusions led to the development of the SAN product family: single-use, disposable, automatic needle insertion devices, with solutions for drugs in plastic or glass luer syringes, prefilled syringe with staked needle, and vials."

The SAN product family is designed for improved patient compliance and adherence to treatment: All SANs reduce needle phobia, anxiety, and pain perception by hiding the needle, ensuring consistent needle penetration depth and angle, preventing needlestick injuries, and allowing for user-controlled injection speed for increased comfort, says Mr. Daily.

The most recent developments are the SAN-DV and SAN-DV Pro. Like an autoinjector, SAN-DV and Pro reduce patient anxiety and are easy to use, says Mr. Daily. Additionally, SAN-DV and Pro simplify the reconstitution process and drug transfer from vials, and allow the patient to control the speed of the injection. Target applications include all drugs in vials – either liquid or lyophilized.

According to Mr. Daily, the SANs product family is:

- Universal – with available solutions for luer syringes (SAN-L), PFS with staked needles (SAN-P), and drug transfer and reconstitution from vials (SAN-DV and SAN-DV Pro);
- Customizable – needle gauges and lengths, vial sizes, and prefilled syringe size (for SAN-P);
- Upgradable – by the option to add connectivity features;
- Green – as they may propose an alternative solution to more complex/large autoinjectors (with less plastic);
- Empowering – the SAN family enables self-injection easily and safely with less anxiety;
- Intelligent – SANs combine features from autoinjectors and prefilled syringes/safety syringes/needles; and
- Likable – the SAN family was found likable and desirable in several formative usability studies by both self-injecting patients and HCPs.

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Gerresheimer—New PFS Addresses Biotech Needs

Gerresheimer Medical Systems produces prefillable syringes and cartridges (primary packaging) made of glass and plastics, as well as customized injection-molded plastic assembly units like insulin pens and autoinjectors.

Gerresheimer plastic experts work with glass specialists to coordinate the tolerances of glass carpules and plastic parts to ensure that injection forces are optimized and that carpule and syringe are positioned optimally in the plastic device.

Gerresheimer currently offers a range of prefillable Cyclo-Olefin-Polymer (COP) syringes produced by long-time partner Taisei Medical Co. Ltd. in Japan. In June 2016, Gerresheimer introduced the Gx RTF® ClearJect® brand, a prefillable plastic syringe with integrated cannula made from high-performance plastic COP for sensitive medications and high-viscosity agents. In the future, American and European customers will be offered COP syringes produced at the German production facility of Gerresheimer Medical Systems.

"COP is an interesting plastic alternative to glass syringes due to the growing demands of novel agents on their primary packaging," says Claudia Petersen, Global Director Business Development, Gerresheimer Bünde GmbH. "COP syringes are resistant to breaking, are as transparent as glass, and hardly interact with the packaged medications. Thanks to the use of injection molding, the design boasts especially tight tolerances. Its precise geometry also reduces dead volume, leaving behind less of the expensive medication in the syringe." Additionally, COP has a high pH tolerance and, unlike glass, does not change the pH value while in storage.

The new 1mL Gx RTF ClearJect syringe is siliconized with a precisely controlled amount of high-viscose silicone oil, which generates lower amounts of subvisible silicone oil particles while providing good functionality, says Ms. Petersen. The design is inspired by ISO 11040-6 and the syringe is equipped with a 27-gauge, 1/2-inch (12.7 mm), thin-walled stainless-steel cannula with three bevels.

Ms. Peterson says the new syringe is economical because the COP body is designed to use commerically available components. This begins with the use of standard cannulas and continues with the piston rods, piston plungers, backstops, and closure systems.

Haselmeier—Flexibility is Key to Next-Generation Devices

As the use of self-administered injection devices grows so does the need to make them more consumer-oriented. Haselmeier looks beyond the functional design and considers the operability, haptics, and ergonomics of the device, the broader "Human Factors" that have a large impact on its use, explains Terence O'Hagan, General Manager, Haselmeier, Inc. "Like consumer products, adoption is driven by product desirability – the style, form, and color selection, combined with ease of use considerations, all make a product (device) more appealing to its owner leading to improved compliance."

A detailed pre-development process is used at Haselmeier to properly evaluate the technical requirements and create devices that are easy and intuitive to use. This structured process allows for engineering and design exploration, as well as Human Factors testing, to verify that the product design will be effective. Combined with a final risk assessment, a complete package is then released for full-scale development.

Haselmeier's D-Flex device is designed to provide a high level of dosing flexibility.

Haselmeier integrates a range of drug cartridges into its pen devices for both disposable and reusable systems. "Understanding the design elements and tolerances of the primary containers and their impact on the device performance and accuracy is paramount when integrating a new package into an existing device," says Mr. O'Hagan. For example, the crimp and stopper dimensions in a 3mL cartridge must be accounted for, and adjustments in the device made, to deliver an accurate dose and expel the appropriate volume. This integration starts early with the execution of a pre-testing program of cartridges before the execution of the platform development.

Haselmeier has announced several new products, including the Axis-D disposable pen, the D-Flex disposable device, and Connected Pens. The D-Flex device is designed to provide a high level of dosing flexibility. "Our initial objective was to design a pen that could be used to inject any dose comfortably, and in which it was possible to set several dose values in steps of any size, without having the annoying intermediate values. There was, and is, no such pen on the market yet," says Joachim Keitel, Head of Strategic Innovation at Haselmeier.

The D-Flex allows for the selection of a series of pre-selected, regular, or non-regular random doses and is designed to prevent the patient from selecting any interim doses.

"The device is appealing to partners with a range of drugs to treat chronic diseases, new biologics, and orphan drugs with very specific dose regimens, and companies developing biosimilars that want a device that improves upon existing devices and can be delivered cost effectively," says Mr. O'Hagan.

Haselmeier's device portfolio is based on specific technology platforms that can be tailor-made for specific drugs and patient populations. For example, the iPen platform delivers insulin, HGH, and parathyroid hormone along with new variants being developed to deliver drugs with orphan designations. And, the new D-Flex platform provides a flexible device where a dose regimen can be changed by modifying a single component.

He explains how one customer was looking for a reusable device to deliver a low-volume fixed dose. In addition, the drug was lyophilized and required reconstitution within a two-chamber cartridge. The indication was to treat a small patient population leading to low device volume requirements. Because of this, leveraging an existing device platform would be more cost effective.

Haselmeier leveraged its iPen technology platform and created a dose limiter within the device set at the specific dose volume, and adjusted the piston rod to accommodate the length of the cartridge and stopper position. A partner provided a mixing device to reconstitute the drug prior to inserting it into the pen.

Finally, the client needed to provide the drug in a range of concentrations. A solution was developed where each concentration was delivered to the patient directly in a color-coded cartridge container. The patient assembled the cartridge container onto the mixing device for reconstitution and transferred the entire container directly to the pen. This simplified the handling procedure with the patient and minimized the potential for errors in using the wrong concentration.

Haselmeier is developing connected technologies that can be applied across its device portfolio, which will allow customers to deliver intelligent solutions for clinical trials, commercial use, or both. "We believe digital medicine can be achieved through intelligent integration of electronic technologies into our existing products versus redesigning our portfolio to meet those objectives," says Mr. O'Hagan.

Insulet—Improving Adherence Through Wearable, Patient-Centric Drug Delivery

With an increasing number of biologics and therapies, pharmaceutical and biotechnology companies face challenges in ensuring the efficacy of a drug, and that patients will comply. This has paved the path for a new future of subcutaneous delivery with a need for intelligent, smart, wearable delivery systems. Additionally, there is also an

With the Omnipod platform, Insulet has created a commercially available, wearable, intelligent, subcutaneious delivery device.

increasing focus on patient centricity—enabling patients greater freedom to live their lives without being restricted by their drug delivery regimen.

"As an industry, we need to better understand pain associated with delivery of different drug types in order to develop these more patient-centric and efficacious devices," says Michael Graffeo, Vice President of Business Development, Insulet Delivery Systems Group. "The push for faster delivery is no longer relevant in the future for drug delivery."

There is also an increasing focus on patient centricity, enabling the patient greater freedom to live their life without being restricted by their drug delivery regimen.

"With more than 800 new highly viscous biologics expected to come to market by 2025, the industry should expect that these drugs will require a device that allows for larger volume delivery over a prolonged injection period," he says. "That's where wearable devices like the Omnipod offer a significant benefit over traditional needles or autoinjectors."

For years, the industry has focused on devices that inject medication in 30 to 60 seconds. Insulet believes that wearable technology changes the dynamic significantly. Since the launch of the Omnipod, Insulet has expanded its wearable pump technology to include multiple drug delivery applications. Insulet has two existing commercial agreements and additional development agreements with several other pharmaceutical companies. "Using our 15 years of commercial success in delivery with our Omnipod platform, we combine that with our partners' knowledge of disease challenges and drug development to tailor a customized solution. These customizations include solutions to suit volume, formulation, delivery requirements, delivery administration, and patient needs," says Mr. Graffeo. "With the Omnipod platform, we have created the only wearable, intelligent, subcutaneous delivery device commercially available."

He continues to explain that the Omnipod platform can modify dosing and delivery times, as well as monitor patient adherence. Additionally, the Omnipod has a remoteless option for preprogrammed dosing regimens. Its auto-cannula insertion means patients never have to handle the insertion needle. Omnipod is discreet, tubeless, and waterproof to help reduce life interference and improve drug adherence.

Medipacs, Inc.—Wearable Device Delivers Biologics Subcutaneously

Medipacs has developed a patent protected, injectable drug delivery technology that is precisely controllable and fully programmable. Medipacs devices are low-cost, low-profile, disposable infusion devices used to deliver drugs subcutaneously, explains Mark Hassett, Vice President, Sales and Business Development, Medipacs, Inc.

Many existing markets (and therapies) can be served today by the Medipacs Mini-Infuser. The patient does not need any special training to use the device, as it is preset to deliver a precise amount of drug to the body over a controlled period of time.

The technology delivers biologics, insulin, hormones, fertility, anti-coagulation, oncology drugs, pain medications, proteins, and

Medipacs Mini-Infuser features continuous subcutaneous delivery and adjustable dosing of biologics.

peptides. "Many of the next-generation biologics will require larger-volume injector systems, which the Medipacs Infuser can also accommodate," says Mr. Hassett.

Medipacs wearable device technology platform offers advantages over other wearable devices, explains Mark McWilliams, Medipacs CEO, such as continuous rate, bolus rate, adjustable dosing, and field fillable options.

"The Medipacs Mini-Infuser/Pump represents the next generation of wearable medication delivery," Mr. McWilliams says. "Medipacs technology platform is transformative and is positioned to lead the reformulation of the IV infusion market by lowering the barriers of injectable drug delivery. They are displacing capital-intensive IV pumps with wearable, disposable devices capable of subcutaneous administrating major drug classes, and changing where patients may now be safely treated, such as outside of acute care settings."

Looking ahead, an Investor Forum Posting (Dec. 2013), entitled *Next Big Thing In Drug Delivery,* states that wearable injectors will be the newest and most appropriate injectable devices for the delivery of the biologics that cannot be administered by patients with standard handheld devices, and further mentions research that estimates more than 350 million wearable devices will be used by 2024.

The market for wearable injectors will involve in excess of 100 pharmaceutical companies with over 250 biologics already approved, or in stage 2-3, explains Mr. Hassett. "The consensus is that if you are investing in a biologic drug, you should also be investing in a wearable injector."

Nemera—Customizable PFS Platform Prevents Needlestick Injuries

Parenteral is often considered as the default route of administration, but is also known as a non-intuitive process. To respond to these issues, Nemera has developed Safe'n'Sound®, a customizable platform of add-on passive safety devices for prefilled syringes, which aims to prevent potential needlestick injuries and facilitate the injection process. The safety feature activates automatically at the end of the injection, easing the use. User interface was integrated at the beginning in the design and development, integrating ergonomic features: a large thumb pad surface to smooth the injection; large built-in finger flange to facilitate handling; a round shape for easy and comfortable handling; a spring located at the syringe flange position to provide good visibility of the tip of syringe; and able inspection of the drug even with low-filling volume drugs. Optional add-on ergonomic extended finger flanges have also been developed to improve the handling, gripping, and comfort for the user, explains Adrien Tisserand, Global Category Manager – Parenteral & CMO, Nemera.

Nemera has also developed a specific version of Safe'n'Sound for subcutaneous injection. This version has only the correct needle length exposed to ensure the drug is administered as intended. And, as rigid needle shield (RNS) can sometimes be a problem, Nemera looked into a technical solution to

Nemera's Safe'n'Sound® for subcutaneous injection and RNS removal feature (left to right).

facilitate RNS removal. The company also developed a 2.25mL version of Safe'n'Sound for self-administering large-volume, highly concentrated, viscous drugs.

A new generation of two-step autoinjector has also been developed for fluid and viscous injections. The Safelia™ autoinjector has been designed to ease the self-injection experience. Safelia delivers formulations in glass syringes, from fluid small molecules to challenging highly concentrated biological formulations in subcutaneous or intramuscular layers.

Mr. Tisserand explains that Safe'n'Sound is a customizable platform of add-on passive safety devices for prefilled syringes. "Even though Safe'n'Sound is compatible with ISO standard syringes (universal) to provide flexibility to pharmaceuticals, customizations could be done to adapt the system to specific syringes. Other routes of customization could be in terms of drug container size, colors, and features (upgradable)."

Noble—Training Devices Help Brands Create Product Loyalty

Noble has developed and launched many new autoinjector and prefilled syringe training devices using a device-comparable approach. This approach means training devices are engineered to replicate the same form and functionality as a real device, including functions like plunger speed, needle simulation, safety mechanisms, and additional technologies that improve proper use and memory recall.

"Noble believes that patients who use trainers will become more familiar with the form and functionality of a real device, demonstrate less self-administration errors, and complete the onboarding process more successfully," says Craig Baker, Executive Vice President of Noble. "Competitive differentiation is both a challenge and opportunity in self-administration drug delivery. As more patients are prescribed self-injection therapies, the need for patient education and training programs will continue to grow."

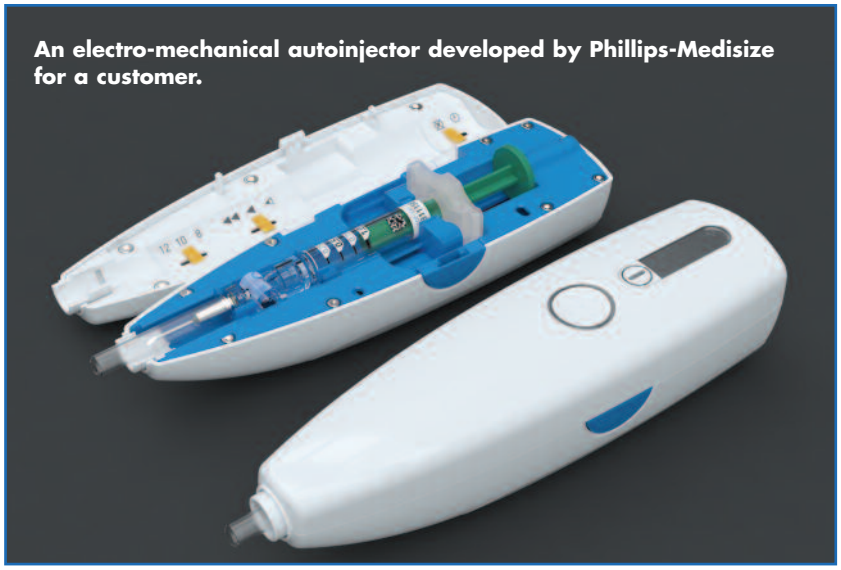
Noble has been involved in many new drug launches, helping brands differentiate themselves through patient support programs. By creating solutions that limit errors, adverse events, complaints, and poor compliance, Noble helps pharma brands overcome the challenges many face with HCP brand preference.

"Brands that provide patients with robust support programs have a higher probability of brand loyalty," says Mr. Baker. "Loyal patients will continue treatment therapies longer, leading to increased market share while also improving patient adherence and outcomes."

Phillips-Medisize—Developing & Manufacturing Injection Devices that Improve Therapy Adherence

The biopharma industry faces new challenges with large-molecule biologics. In particular, a large volume of a viscous solution requires special care to ensure proper dosing and customized injection devices. A more complex therapy regimen risks lower adherence and persistence rates and ultimately reduced patient outcomes. Phillips-Medisize focuses on the development and manufacture

As a complete training solution for the biopharma industry, Noble helps brands with competitive differentiation through patient support programs geared to help patients successfully onboard and maintain adherence.



An electro-mechanical autoinjector developed by Phillips-Medisize for a customer.

of injection systems that improve therapy adherence and persistence in terms of injection speed, dose volume, and date/time of delivery.

"As a contract designer, developer, and manufacturer, we work closely with customers to develop and manufacture a range of injection devices, from mechanical autoinjectors and pen injectors to microneedle injection devices, needle-free injectors, and electro-mechanical injectors for various therapies," says Bill Welch, Chief Technology Officer, Phillips-Medisize.

Mr. Welch adds that the trend towards self-administration has resulted in the growth of electronics integration and Human Centered Design to support adherence, persistence, convenience, and patient safety. Phillips-Medisize's integrated product development process, combining Human Centered Design principles with a solid design for manufacturing philosophy, improves the probability of success for our customers," he says. "Devices are getting smaller and smarter. As a result, we engineer compact and portable devices that allow discreet usage and improve adherence."

Having a strong background and history in device strategy enables Phillips-Medisize to understand user needs and find ways to optimize the therapy solution. One example is a connected health solution for a leading pharma customer who asked the company to create a device strategy for a mature Multiple Sclerosis drug. The strategy work identified an opportunity to deploy a connected health solution.

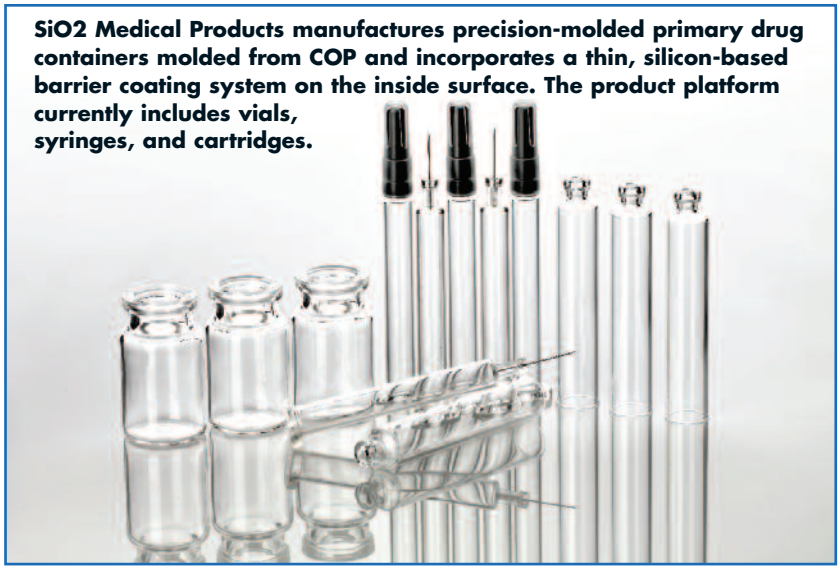
The outcome was an intelligent injection system to support treatment adherence. It consists of an electro-mechanical connected autoinjector, a software application for patients, and a dashboard for physicians and nurses that securely displays user treatment data from the system's software cloud. "We developed the first range of conceptual designs based on a draft target product profile document received from the customer expressing some of the key ideas and mandatory requirements," explains Mr. Welch. "We were responsible for the conceptual program and the subsequent full development program. From the start, there was a clear strategy that we would develop the product (device) and connected service, manufacture it, and supply to the customer the complete packaged product ready for distribution to global markets."

In this and other projects, Mr. Welch says the company's philosophy of a successful design must be usable, intuitive, and desirable to minimize risk of error, increase adherence, and ensure the device fits into the user's lifestyle.

SiO2—Addressing Unwanted Interactions Between Drugs & Packaging

Traditional borosilicate glass syringe barrel and plunger components have been implicated to introduce unwanted interactions between the therapeutic drug product and component materials. For example, silicone oil has been reported to denature proteins and form protein aggregates. Similarly, leachable metal compounds can oxidize and aggregate proteins.

SiO2 Medical Products has taken a system approach toward addressing unwanted interactions between therapeutic drugs and their packaging. The syringe barrel is composed of a medical-grade COP coated with an inert and dense



SiO2 Medical Products manufactures precision-molded primary drug containers molded from COP and incorporates a thin, silicon-based barrier coating system on the inside surface. The product platform currently includes vials, syringes, and cartridges.

silicon-based barrier system that does not allow leachable and extractable compounds to interact with the drug formulation, explains SiO2's Chief Scientist, Dr. Christopher Weikart. "Similarly, an innovative plunger was developed that eliminates silicone oil and provides an inert and leachable-free drug contact surface." Vial, syringe, and cartridge products are highly customizable due to the inherent flexibility of both the molding and coating processes.

"Each product meets the highest level of dimensional tolerance that cannot be achieved by traditional borosilicate glass processing," says Dr. Weikart. The vacuum-based plasma coating process is highly adaptable to complex shaped articles irrespective of packaging size and aspect ratio. The coating system, which is about 250 times thinner than a human hair and completely conformal, has an insignificant impact on the dimensions and internal volume of the packaging.

"Managing, controlling, and ultimately reducing intrinsic and extrinsic particulates in parenteral packaging is an ongoing opportunity for improving the quality of drug products," says Dr. Weikart. "Ultimately, unwanted particulates can lead to therapeutic drug-to-particulate interactions that can result in dangerous immunogenic responses in patients. Continuous improvement in the materials of construction of primary packaging, secondary packaging, and complete elimination of silicone oil lubricants would be a major step in the right direction for the pharmaceutical industry as a whole."

Sensile Medical—Human Interface Eases Use for Patients & Caregivers

Human factor considerations are playing an ever-increasing role as novel drug delivery systems are coming to market. Healthcare professionals, patients, and caregivers need to safely prepare, place, activate, and remove the device with minimal difficulty.

The SenseCore technology allows for single-button operation with visual and audible signals that are easy to understand, says Sandra de Haan, Head Business Development at Sensile Medical. The user interface can also incorporate a colored touchscreen display, multiple language packages, etc. The devices can be pre-programmed for the desired drug delivery profile at the time of manufacturing. Alternatively, if the therapy requires a weight-based delivery, adjustment programming can be done by the doctor or patient.

"Sensile Medical offers early-stage compatibility testing to de-risk the compatibility issues from the start," explains Ms. de Haan. "Materials in contact with the drug product are carefully chosen and undergo all necessary testing."

Sensile Medical has developed a micro-pump, which is the heart of all of its devices. Its next product will be a large-volume body-worn patch pump for its partner scPharmaceuticals with Furosemide. "The overall objective for the development of the device was to offer the most advanced features for safety and convenience, with the cost and utility of a disposable product," says Ms. de Haan.

SenseCore technology allows for the development of a small two-component device comprising a single-use disposable unit and a reusable unit. This concept offers several advantages: The design of the disposable unit enables a cost-

Sensile Medical's large-volume patch pump 20mL.

efficient, high-volume production process, she says. Using just two plastic parts for the SenseCore technology supports keeping the costs at a low level.

With Sensile Medical's disposable/reusable concept, there is no need to discard the entire device after use, as the mechanism that provides the force and energy is part of the reusable unit. "This reduces costs and leads to less waste."

Additionally, the priming process is automatic and does not require separate handling steps. This integrated feature increases safety, saves time, and helps prevent errors by HCPs, patients, and caregivers, Ms. de Haan says.

Terumo®—Tapered Needle Technology (TNN) Combines Injectability & Patient Comfort for Highly Viscous Biologics

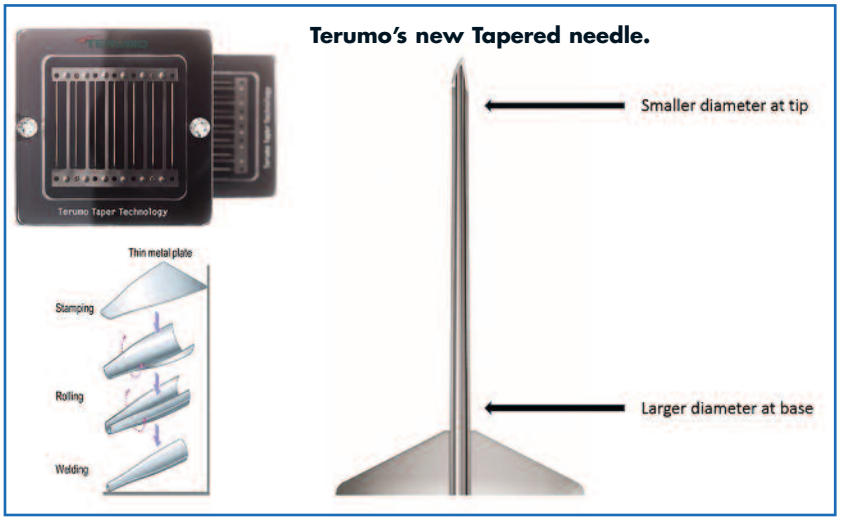
In 2005, Terumo® launched the 33 gauge (G) x 4 mm Nanopass pen needle (not available in US and Canada) to provide better injection comfort for diabetic patients who have to self-administer daily insulin injections. This micro-tapered needle had larger diameter at the distal end and a smaller diameter at injection tip. Based on the same principles, Terumo launched the 34G Nanopass (not available in the US and Canada) pen needle.

"Micro-tapered technology is very useful for hypodermic needles and staked needles to deliver viscous and/or concentrated protein solution/suspension that usually require either dilution or additional devices (e.g. large volume injector)," explains Sagarika Bose, PhD, Senior Manager in Technology Development, Terumo Pharmaceutical Solutions, Terumo. "With a thinner needle, we expect better patient comfort."

The impact of a tapered needle is significant as formulation scientists can load more drug into the formulation, which may reduce the frequency of administration, says Dr. Bose. "Usually higher concentration of drug leads to higher viscosity. The formulation either needs to be diluted or large-volume injectors are required. Tapered needle technology combines the effects of diameter and length to provide lower glide forces for viscous drug products, including concentrated protein biologics. For example, 29-24G tapered needle has 24G needle at the base and 29G needle tip. This gauge reduction in needle size facilitates reduction of the glide forces during injection. The 29-24G taper needle reduces glide force by approximately 46% when compared with same gauge straight needle for viscous biological product.

"This novel needle technology may be used to achieve better patient compliance with a smaller needle at the tip when injecting viscous drug products," she says.

Terumo aims to deliver medications safely and reliably, ensuring the efficacy of treatment, patient adherence and outcome, while minimizing patient trauma, pain, and discomfort, she says. To achieve that goal, Terumo offers a "pain evaluation service" that helps pharmaceutical companies optimize their drug formulation (e.g. pH, ionic



Terumo's new Tapered needle.

strength, viscosity, etc.) and device variables (e.g. needle size, speed of injection, angle of injection, etc.) to reduce pain from injection in patients. With Terumo's "pain evaluation service," quantification of pain from needle insertion and/or drug injection in animal models allows pharmaceutical companies to understand the pain experiences during injection.

The Tapered needle can be used with PLAJEX™ syringes. PLAJEX (COP polymer syringe) is a ready-to-use prefillable syringe with i-coating™ technology on the plunger stoppers to create a silicone oil-free system. It is also free of tungsten and glue and has low sub-visible particles. These advantages can decrease the risk of protein aggregation in biologics. At the same time, the use of steam sterilization can reduce protein degradation through oxidation (which can happen from sterilization by irradiation as a result of free radicals generation). PLAJEX is available with or without tapered needle. The PLAJEX and tapered needle combination can provide better drug/device compatibility, says Dr. Bose.

Tapered needle and PLAJEX (individually or together) are in testing for many pharmaceutical companies to solve the issues of high concentration/viscosity in injectable products, as well as can reduce the risk of protein aggregation. "Pharmaceutical companies can avoid the potential cost and complication due to dilution (with additional devices) and may reduce the risk of protein aggregation by using tapered needle technology and PLAJEX."

West—Developing Devices Based on the Patient Experience

With the continued emphasis on biologic drugs, and the assumption that most of them will require injection (in many cases by the patients themselves), West continues to focus on improving the "patient experience" through a combination of four key elements: 1) a thorough understanding of patient/user needs; 2) the design, development, and manufacture of patient-centric delivery systems; 3) ensuring effective training and onboarding; and 4) encouraging and tracking adherence.

As an example, a recent study by patient onboarding company Noble, and analyzed by Auburn University, found that more than 60% of patients self-reported that they did not thoroughly read the required steps outlined in a self-injection system's "Instructions for Use" document prior to beginning drug treatment. By not following instructions, there is significant potential for administration errors that can impact compliance, which can have a negative impact on a patient's care, says Graham Reynolds, Vice President and General Manager, Biologics, West Pharmaceutical Services, Inc.

To address this area of the adherence challenge, West and Noble have teamed up to offer validated training for all self-administration systems to West's pharmaceutical and biotechnology customers. In the training, West brings its expertise in human factors testing and analysis to the design of drug delivery systems, and Noble incorporates similar human factors principles into the development of Instructions for Use, onboarding, smart training devices, and packaging. "Through this collaboration we aim to help improve the patient experience, provide training to reduce administration errors, and help patients keep compliant with their prescribed

West's SmartDose® technology platform.

treatment," says Mr. Reynolds.

With the increasing demand for combination products, it is essential to fully understand the interaction between the four key elements of an effective drug delivery system—the drug, the container, the delivery device, and the patient. Starting with the drug and container, it is becoming even more critical that the interaction between the two is fully understood to minimize interactions, reduce and control extractables/leachables, and reduce the presence of particles. Selection of the container should also be considered with regard to the final delivery method.

"We are more focused than ever on delivering high-quality components that are designed to reduce particulate, ensure consistency of delivery, and fit the changing needs of higher-volume delivery systems," says Mr. Reynolds. "Earlier this year, we introduced a new packaging solution to address the need for greater quality in injectable components and help protect the safety, efficacy, and purity of advanced biologics: the 1-3mL NovaPure® plunger. This innovative, high-quality component was specifically created for higher-volume prefilled delivery systems."

West designed and manufactured the 1-3mL NovaPure plunger using Quality by Design (QbD) principles to ensure dimensional control and consistency, sub-visible and visible particulate control, and low parts per million (ppm) defect attributes. Featuring optimized breakloose and glide force profiles, 1-3mL NovaPure plungers are designed to deliver consistent functional performance for autoinjector applications across various injection volumes, including as part of increasingly common 2.25mL injectable drug delivery systems, Mr. Reynolds says.

He continues: "A QbD approach delivers an improved, data-driven output that can lead to a superior product, and also leads to a process that allows stakeholders to better understand risk and how to minimize it. Utilizing a QbD approach helps to minimize disruptions to the supply chain and bring safe, effective drug products to market – and to the patient – quickly and efficiently."

West partners with a number of customers to create integrated drug delivery systems that meet their needs for ensuring safe and effective treatment and help to improve patient outcomes. As one example, Amgen selected the SmartDose® technology platform for a new single, monthly 420mg dose delivery option for Repatha® (evolocumab).

The SmartDose technology platform was developed with extensive human factors testing and analysis to understand the interaction between the patient and the delivery system, explains Mr. Reynolds. "SmartDose technology adheres to the patient's body, usually on the abdomen, so patients can be hands-free while self-administering medication in accordance with their prescribed treatment."

The SmartDose technology platform is an integrated solution of delivery and containment featuring a silicone-free Daikyo Crystal Zenith® cartridge and a Flurotec® coated piston containment system. Its design allows the dosage amount and length of time to be pre-programmed to the drug maker's specifications. Beyond the actual delivery, the aesthetic features of SmartDose technology, such as color scheme, can be customized to maintain branding.

Ypsomed—Building a Platform that is Cutomizable to Meet Current & Future Needs

In the world of self-injection devices, ergonomics is key to improve patients' compliance. Ypsomed uses human factor engineering methods throughout the development cycle of its products. Examples of Ypsomed's platform products are YpsoMate, the 2-step autoinjector, and UnoPen, a disposable pen, both of which have been tested for usability in extensive formative human factor studies on a platform level. "With these studies we prove the usability of our platform products, even before the implementation of further ergonomic modifications during the customization to the customer-specific product," says Simon Michel, CEO of Ypsomed.

To address the trend towards less frequent injections and increasing injection volumes, and higher payloads that need to be delivered in one injection, the YpsoMate 2.25 allows the injection of up to 2.25mL and has enough power to inject

From left to right: UnoPen disposable pen; YpsoMate, the 2-step autoinjector; LyoTwist, the intuitive dual-chamber device; YpsoDose, a next-generation large-volume injector (Ypsomed).

viscous liquids within a short period of time. "Its two-step operation, and visual and audible feedbacks give the patient confidence in handling the device," says Mr. Michel.

Ypsomed is also active in the new device class of large-volume injectors that complement pens and autoinjectors. YpsoDose is a prefilled, fully disposable, electro-mechanical patch pump that has an auto-insertion needle mechanism, a glass container with a sterile fluid path. YpsoDose covers the range of injectable volumes from 2-5mL.

Preparing and injecting a drug that is not liquid stable is a problem for self-injecting patients. Preparing the drug for injection requires the patient to perform a number of steps that are prone to handling errors. An example of a drug that is not liquid stable is long-acting GLP-1 as used by diabetics. Compared to daily-injected GLP-1, long-acting GLP-1 products are injected once a week, but need to be reconstituted before injection. To eliminate the difficult preparation steps, Ypsomed provides LyoTwist device technology for simple reconstitution. The key to the system is a dual-chamber cartridge that holds the lyophilized drug or drug powder and the solvent in separate compartments. With a simple twist, the drug is reconstituted and the air is removed from the system. The drug is injected by pushing the injection button. LyoTwist is available with manual or automatic injection and with fixed or customizable variable dosing. AstraZeneca and GSK both recently launched their long-acting GLP-1 products in customized versions of LyoTwist.

Thanks to the modality of the Ypsomed custom product platforms, they can universally be used for a number of drugs and indications, he says. "The platforms allow not only customization to the properties of the drug and primary packaging container, but also the customization of design," says Mr. Michel. "With this option, it is possible to upgrade the device for certain patient groups that require special support in the handling process. Clever platform products provide the mechanical interfaces with the smart technologies. This allows customers to easily upgrade their device with smart technologies without changing the basic design of the device." ◆

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THERAPEUTIC FOCUS

Ischemic Stroke: Treatment Beyond the First 3 Hours

By: Rick Pauls, MBA

INTRODUCTION

Strokes are the third leading cause of death in the United States and the leading cause of disability. Almost 800,000 Americans suffer a stroke every year; that's a rate of one every 40 seconds. About 20% of strokes are fatal. Worldwide, strokes cause about 5 million deaths annually and leave another 5 million disabled. Smoking, high blood pressure, age, and atrial fibrillation are major causes of strokes.

There are two types of stroke: hemorrhagic and ischemic. A hemorrhagic stroke occurs when a blood vessel in the brain ruptures. Uncontrolled hypertension is the main cause of such strokes, but weakened blood vessels that usually cause hemorrhagic stroke are either aneurysms or arteriovenous malformations. Surgical treatment may be done to stop the bleeding. If the bleed is caused by a ruptured aneurysm (swelling of the vessel that breaks), a metal clip may be placed surgically at the base of the aneurysm to secure it, or the stroke can be prevented by shoring up the weakened vessel with a catheter that deposits a mechanical agent, such as a coil, to prevent rupture.

Ischemic strokes account for 87% of the total number of strokes. Related to them are "transient ischemic attacks, or TIAs, events wherein a clot temporarily blocks blood flow. These "mini strokes" are warning signs that need to be taken seriously.

tPA – THE GOLD STANDARD FOR ISCHEMIC STROKE TREATMENT

The gold standard for treatment of ischemic strokes is tissue plasminogen activator, or tPA, also known as IV rtPA, given through an IV in the arm. tPA is the only FDA-approved treatment for ischemic stroke. tPA works by dissolving the clot and improving blood flow to the part of the brain being deprived of blood flow. If administered within 3 hours (and up to 4.5 hours in certain eligible patients), tPA may improve the chances of recovering from a stroke.

For some patients who have already received tPA treatment, an additional endovascular procedure may be an option. In a mechanical thrombectomy, a trained doctor will try to remove a large blood clot by sending a wired-caged device called a stent retriever to the site of the blocked blood vessel in the brain. To remove the brain clot, doctors thread a catheter through an artery in the groin up to the blocked artery in the brain. The stent opens and grabs the clot, allowing doctors to remove the stent with the trapped clot. Special suction tubes may also be used. The procedure should be done within 6 hours of acute stroke symptoms, and only after a patient receives tPA.

A significant number of stroke victims don't get into the hospital in time for tPA treatments. tPA must be administered within 3 hours to ensure it has maximum effect because after the first few hours, the damage to sensitive brain tissue has

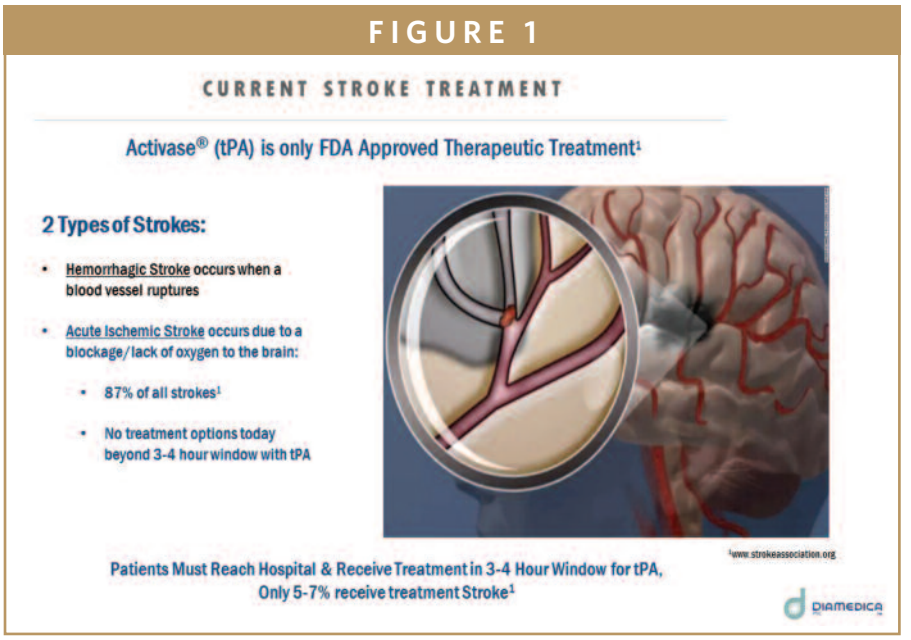
already been done time is brain). As a result of this ticking clock, only 5%-7% of ischemic stroke patients receive tPA in time. For the others, medical attention comes too late. This is why it's so important to identify a stroke immediately.

WIDENING THE TREATMENT WINDOW

Obviously, a therapy that could extend that window would offer treatment options for any additional patients and improve outcomes immensely. However, finding better alternative treatments has been challenging. There have been only three positive Phase III randomized clinical trials in acute ischemic stroke, all reperfusion therapies (NINDS; PROACT II; ECASS III), and only tPA has FDA approval.

One way to possibly widen the treatment window is to improve tPA itself. Researchers explored the use of tenecteplase (TNK) tPA to safely treat this type of stroke (intracranial occlusion) before it progressed. The research presented during the American Stroke Association's 2015 International Stroke Conference (ISC) in Nashville, TN, used TNK as opposed to alteplase. TNK is a mutant tPA with a longer half-life and higher fibrin specificity. Reports suggest TNK may be easier to administer and may have lower risks for intracranial bleeding. The research has yet to reveal whether TNK offers a much wider window.

FIGURE 1



STEM CELLS AS A MAGIC BULLET

Another option is to find something that works better than tPA, allowing for more time between the event and the treatment. Stem cells have been pitched as the magic bullet for numerous conditions for years. In the case of ischemic stroke, one company has actually made some headway in using them to widen the window. Athersys has a stem cell therapy called MultiStem, an IV administration treatment that uses stem cells from a donor to regenerate damaged blood vessels. In February 2016, it released the 1-year results from its ongoing follow up to a Phase II trial in its lead indication of strokes. A Phase II trial is scheduled to start before the year is over.

EXOTIC SOURCES FOR A TREATMENT

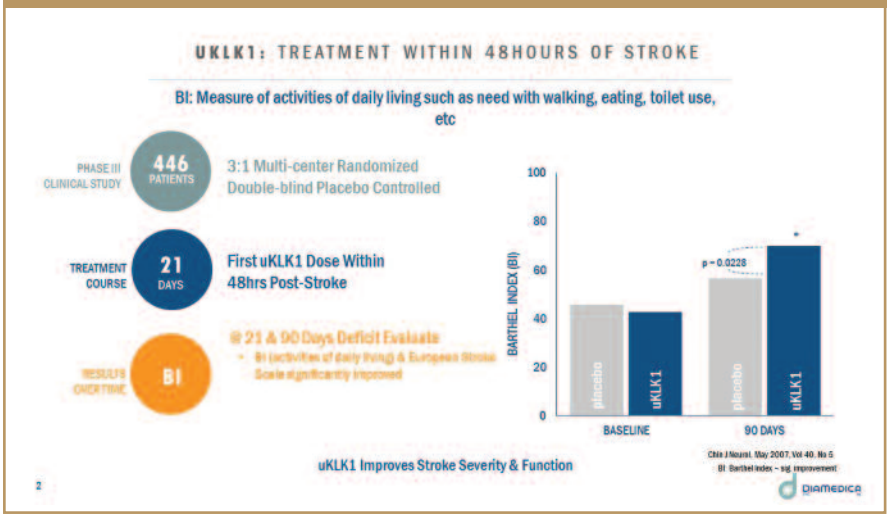
Researchers have gone to great lengths to find ways of widening the stroke-treatment window. In December 2008, Neurobiological Technologies abandoned clinical trials of Viprinex™, derived from the venom of the Malaysian pit viper, for the treatment of acute ischemic stroke because they were unlikely to show benefit.

At Northeastern State University in Oklahoma, researchers have grafted DNA from bats into tobacco plants to create a protein that breaks up blood clots. To the unvitiated, this may sound bizarre, but tobacco plants were used to treat Ebola just last year.

"Vampire bats lick the wound of an animal to keep it from clotting, so that they can keep drinking from that blood," graduate student Damien Hall said. "Using that concept, using their saliva to keep a stroke from clotting in order to keep someone alive is almost the same."As the plants grow, a protein develops inside the leaves. The leaves are eventually ground up, filtered and turned into the drug that can be injected into patients shortly after a stroke. "As soon as it touches the clot, that protein dissolves that clot," Hall said.

After vipers and bats, urine-sourced products don't seem that strange. A urine-extracted form of the kallikrein-1

FIGURE 2



("KLK1") protein, trade name Kailikang®, has been approved for the treatment of acute ischemic stroke in China. DiaMedica estimates over 40,000 patients are treated each year.

DM199 FOR ACUTE ISCHEMIC STROKE

DM199 is a recombinant form of the kallikrein-1 (KLK1) protein. DiaMedica, which produces DM199, believes its drug offers significant benefits over the urine-sourced product, including the removal of any product supply constraints, very low manufacturing costs, reduced risk of endotoxins, and a product capable of meeting the regulatory requirements for worldwide use. A subcutaneous formulation of DM199 may also make the treatment much easier to administer compared to intravenous administration. Diamedica believes DM199 could widen with treatment window to as much as 48 hours, and when used in combination with tPA, the results could be even better.

DiaMedica has completed several safety and toxicology clinical trials with DM199, establishing an excellent safety record with its single-ascending and multiple-ascending dose trials. DM199 has also established maximum dose-limiting tolerability of orthostatic hypotension at the very high dose levels, which is expected and consistent with the mechanism. There was no anti-drug antibody response after 28 days of therapy, and the formulation is free of endotoxin complications. DiaMedica is preparing a bridging clinical study to select the dose comparable to the approved Kailikang® dose.

TIME IS STILL BRAIN

The treatment of ischemic strokes hinges on getting tPA into the patient within just a few hours of the stroke occurring. The drug works, of that there is no doubt – but getting to the hospital in time for it to work quickly requires a great deal of luck. Anything that buys the patient more time is worth pursuing. Time lost is still brain lost. ◆

To view this issue and all back issues online, please visit www.drug-dev.com.

BIOGRAPHY

Rick Pauls was appointed President and CEO of DiaMedica in July 2009 and has been Chairman of the board of directors since 2008. Mr. Pauls was previously the Co-Founder of CentreStone Ventures Inc., an early stage life sciences venture capital fund. While with CentreStone, Mr. Pauls led the investment in DiaMedica and Sanomune Inc., both named among Canada's Top 10TM Life Science Companies and LED Medical Inc., winner of Red Herring Canada 50 award in the Health category. Prior to CentreStone, he was with Centara Corporation, another early stage venture capital fund. Prior to his involvement with venture capital, Mr. Pauls specialized in asset-backed securitization and structured finance at the General Motors Acceptance Corporation in Minnesota. He earned his BA in Economics from the University of Manitoba and his MBA in Finance from the University of North Dakota.

Drug Development
EXECUTIVE

Dr. Stephan Kutzer
CEO, President & Chairman
Alcami

ALCAMI: Delivering Solutions by Connecting at Every Level

AAIPharma Services Corp. and Cambridge Major Laboratories, Inc. have joined to form Alcami Corporation, a world-class solution provider and supplier of comprehensive pharmaceutical development and manufacturing services. The company's transformation is reflective of current outsourcing trends in which small and mid-size pharma and biotech companies have eclipsed larger companies to become the leading outsourcers for new clinical compounds. With seven sites across the globe, Alcami's combined capabilities include API development and manufacturing, solid state chemistry, formulation development, analytical development and testing services, clinical and commercial finished dosage form manufacturing (oral solid dose and parenteral), packaging, and stability services. Alcami is committed to working seamlessly and tirelessly to ensure they aid in the clinical progression and commercialization of medicines for their customers. *Drug Development & Delivery* recently caught up with Dr. Stephan Kutzer, CEO, President, and Chairman of Alcami, to discuss his company's business strategy, outsourcing trends, how Alcami meets the growing needs of customers, and why companies choose Alcami.

Q: Can you please tell our readers more about Alcami?

A: Alcami is an industry-leading CDMO that strives to be the premier "end-to- end" world-class solution provider that aids in the development and manufacturing of safe and reliable medicines for our customers' patients. We provide flexible, transparent, and innovative services to small and mid-size pharma and biotech companies by offering individualized and integrated services across APIs, solid and sterile drug product, development, analytical testing, and regulatory services. Our development and manufacturing facilities are located in Germantown, WI, Wilmington, NC, Charleston, SC, St Louis, MO, Edison, NJ, Durham, NC, and Weert, the Netherlands. The sites are supported by greater than 1000 employees.

Q: What is Alcami's business strategy?

A: Our offering is focused on the connection between a CDMO and customer, and our strategy is to be focused on individualized and end-to-end service for the right audience. We target a mix of projects across all clinical phases and commercial. It is our goal to have a balanced portfolio with a heavy focus on the clinical supply. We believe our sweet spot is to provide development and manufacturing solutions for small- to mid-size volume products being developed by small- to mid-size pharma and biotech companies.

We are first focusing on ensuring our company is truly integrated and acts as one company. This is one of the most important factors in ensuring we can execute an end-to-end offering. In addition, we believe our key differentiators and ability to execute an integrated offering is our Program Management function – we are building an organization that provides a single face to the customer. We are also creating a "playbook" that outlines all the necessary steps, interactions, and expectations to seamlessly execute an end-to-end project. We have officially launched our first integrated offering (ProForm Select™) that covers solid-state chemistry and formulation development.

In addition, the company has successfully manufactured and released GMP API through sterile drug product late-stage clinically packaged material within 79 days. Alcami's fully integrated methodology delivered the materials 65% faster than the industry's non-integrated approach, which can take more than 230 days.

The aforementioned example directly ties to our commitment to becoming an industry-leading end-to-end service and solution provider. This is the first time the company has produced both GMP API and GMP drug product in continuous end-to-end fashion, and completion time can be reduced even further. Through value stream mapping, the company's Operational Excellence group in collaboration with Operations, Quality, Development, and Commercial has identified further potential ways to decrease manufacturing release time to <55 days and fully released clinically packaged material in less than 60 days.

Q: How do current outsourcing trends impact what Alcami does in the future?

A: The current outsourcing trends have meant that 60% to 70% of new clinical compounds originate from small and mid-size pharma and biotech companies. This trend is directly linked to the funnel of new products that are expected to commercialize over the years as they progress through clinical trials.

Therefore, it is of utmost importance that the focus be on providing these customers with technology and supply chain solutions that are tailored to getting these new candidates through the clinic as fast as possible. Alcami provides tailored offerings for these small and mid-size organizations with individualized and integrated services across APIs, drug product, development services and analytical testing. We are experienced and specialized in taking a molecule to market for these types of current outsourcing trends.

"Alcami is built on the strength of our science, technology, regulatory, and program management know-how. We bring superior science and full attention to every stage. We provide leading technological solutions to successfully aid clinical programs, as well as launch and produce early commercial supply."

Q: What investments is Alcami making to better meet the needs of customers?

A: Alcami is committed to project onboarding and capacity enhancements to better meet customer needs. To improve our Drug Product Sterile site in Charleston, Alcami has added a second line for GMP batches, a new mid-scale lyophilization unit, and a third manufacturing shift. At the Drug Product Oral Solid Dose site in Wilmington, new equipment and a second manufacturing shift has increased capacity by approximately 35%. In Development Services, 5,000 sq ft of lab and lab support area is to be added in 2016, expandable to an additional 40,000 sq ft in 2017 and beyond. For API Germantown, there will be a capacity increase of 50% across kilo-labs, clinical, and commercial manufacturing. In API Weert, plans are made to increase capacity by 50% across kilo-labs and 30% across clinical manufacturing. Alcami's Analytical Testing will relocate to a state-of-the-art new facility at the Cortex Innovation Center in St. Louis in the first half of 2017. Additionally, Alcami has implemented Saturday operations for sample receipt and testing operations at all three sites, which will increase capacity by 20% per site.

Over the last 5 years, the combined company has invested over $100M in capital (~$20M/year), which has positioned us for continued double-digit business growth for the foreseeable future. We plan to continue to make strategic investments into the business as supported by market needs.

Q: Why do companies choose to work with Alcami?

A: We strive to be connected at every level between the customer and us, ensuring there is connection from early stage to late stage, and expertise is connected across development and manufacturing. We are connected intellectually, scientifically, and philosophically to our customers at every level of their organization. We cultivate a relationship from the onset to allow for a transparent and open communication between the customer and CDMO that is based on trust, and the foundations lie in communications, flexibility, philosophy, and personalities.

Alcami is built on the strength of our science, technology, regulatory, and program management know-how. We bring superior science and full attention to every stage. We provide leading technological solutions to successful aid clinical programs, as well as launch and produce early commercial supply. Alcami is focused on servicing our clients in areas where others fail. We want a diversified and broad portfolio of products across all clinical phases and indications.◆

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Technology & Services Showcase

DPI Capsules

Ezeeflo

ACG Associated Capsules Pvt Ltd (ACG ACPL), part of **ACG Worldwide**, is the world's second largest manufacturer of empty hard gelatin capsules. Mechanisms for Dry Powder Inhalation require capsules that offer low powder retention, low microbial count and moisture content, and efficient puncturing and puncturing performance on the most popular capsule-based DPI devices. ACG ACPL has been serving customers worldwide with Ezeeflo – a unique capsule meant specifically for inhalation formulations used in any type of Dry Powder Inhalation devices with a special procedure. Ezeeflo is available in both gelatin and HPMC material, in varied colors, and also available in size 3. Ezeeflo is manufactured with the highest standards of quality at ACG ACPL's world-class manufacturing facilities that are ISO and WHO GMP certified. For more information, visit ACG ACPL at **www.acg-world.com**.

Innovative Products

ADARE Pharmaceuticals™

Adare is a global specialty pharmaceutical company focused on developing innovative products that can improve the lives of patients whose treatment needs are not fully addressed by current medications. With extensive experience across a broad range of therapeutic areas, Adare is actively pursuing growth in its proprietary pipeline, including development, acquisitions, and expanding its GI portfolio with its natural bacterial product franchise. By applying its capabilities and expertise, Adare provides innovative solutions that help solve a broad range of challenges for patients around the world. Adare experts can help you overcome complex formulation challenges and add valuable IP to commercialized products and products in development. Experience a partnership focused on the needs of patients and your company's goals. For more information contact Adare at **BusDev@adarepharma.com**.

CDMO

Alcami is a new CDMO you already know. AAIPharma Services Corporation and Cambridge Major Laboratories, Inc. have joined to form Alcami, a world-class supplier of comprehensive pharmaceutical development and manufacturing services headquartered in Wilmington, NC. Operating at seven sites in the United States and Europe, our combined capabilities include API development and manufacturing, solid- state chemistry, formulation development, analytical development and testing services, clinical and commercial finished dosage form manufacturing, packaging, and stability services. Combining two companies into the strength of one, we offer a unique end-to-end outsourcing opportunity. Streamline your engagement to a single team experienced in taking products to market. We're easy to work with, and a less fragmented approach for your project mitigates risk and shortens timelines. For more information, visit Alcami at **www.alcaminow.com**.

Elastomeric Closures

Aptar Stelmi designs and manufactures elastomeric closures: stoppers for vials, and prefilled syringe and cartridge components, such as plungers, needle shields, and tip caps for all parenteral applications. PremiumCoat™ is a novel range of elastomeric stoppers developed by Aptar Stelmi. Based on an approved, pure, state-of-the-art formulation, the surface of the elastomer is coated during manufacturing with an ETFE film. This coating acts as an effective barrier to many of the extractables and leachables that can be released from the elastomer. As a result, compatibility of the drug and the closure is significantly superior with PremiumCoat™ stoppers. Our first design to be released in 2015 was a 20 mm coated stopper. We are now widening our PremiumCoat™ range with a 13 mm coated stopper and will soon extend our offer with other products. For more information, visit Aptar Stelmi at **www.aptarstelmi.com**.

Technology & Services Showcase

Innovative Dosage Forms

Capsugel®

Capsugel designs, develops, and manufactures a wide range of innovative dosage forms for the biopharmaceutical and consumer health & nutrition industries. Our unique combination of science, engineering, formulation, and capsule expertise enables our customers to optimize the bioavailability, targeted delivery, and overall performance of their products. We partner with more than 4,000 customers in over 100 countries to create novel, high-quality, and customized solutions that align with our customers' evolving needs and benefit patients and consumers. For more information, visit **www.capsugel.com**.

OptiForm® Solution Suite

Catalent's OptiForm® Solution Suite was launched in 2015, and combines both predictive and high throughput screening technologies to identify the most stable and efficient drug form for small molecules. By matching the best drug delivery technologies to each developmental molecule, optimal preclinical PK materials can be delivered in just 12 weeks. OptiForm Solution Suite Bio extends the rapid screening technology platform to include macromolecules, and the identification of suitable non-invasive methods of drug delivery for biological drug products. Expanding the scope to encompass macromolecules, OptiForm Solution Suite Bio employs Catalent's OptiGel™ Bio and Zydis® Bio advanced formulation technologies, and uses a parallel screening model, based on rigorous science and best-in-class formulation expertise, to deliver in vivo study material in as little as three weeks. For more information, contact Catalent Pharma Solutions at (888) SOLUTION or visit **www.catalent.com.**

Differentiated Injectable Delivery

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

Super Refined™ Excipients

CRODA

Croda manufactures a complete range of high purity excipients and delivery aids, offering superior quality for the global pharmaceutical market. These excipients are ideal for multiple dosage forms, including topical, parenteral, oral, and ophthalmic formulations as well as advanced delivery systems. Croda's Super Refined™ excipients go through a proprietary process to remove the polar and oxidative impurities that can cause performance and stability issues. These excipients are ideal for use when working with sensitive drug actives, helping to maximize the stability and overall performance of the drug product. Excipients in the Super Refined range include PEGs, polysorbates, oils, and triglycerides, propylene glycol, castor oil, and a range of topical penetration enhancers, such as oleic acid and dimethyl isosorbide. For more information, contact Croda at (732) 417-0800 or visit **www.crodahealthcare.com.**

Technology & Services Showcase

On Body Delivery System

Enable Injections' on body delivery system (OBDS) delivers high-volume, often viscous drugs subcutaneously for patients to conveniently and discreetly inject at home, work, or on the move. The design is based upon over 12 years of research in minimizing injection pain with a strong emphasis on the end-user and Human Factors. The platform consists of a single injector up to 5-ml, 10-ml, 20-ml, 30-ml, 40-ml, 50-ml capacity - and associated transfer system. One of the three transfer systems (Syringe, Vial, or Fully Automated Reconstitution) is combined with each injector to provide the user with a simple disposable package. This package transfers the drug from the original container closure to the injector in a few intuitive steps. For more information, visit Enable Injections at **www.enableinjections.com.**

COP RTF Syringe

Gerresheimer already offers a range of ready-to-fill COP syringes manufactured by its long-standing partner, Taisei Medical Co. Ltd., in Japan. In this partnership, Gerresheimer's role is to market the ClearJect syringes and provide technical support to customers in Europe and America. Now the company has extended its COP syringe portfolio by combining its glass RTF (ready-to-fill) concept with ClearJect to create the new Gx RTF ClearJect brand. The new syringe will be manufactured at the Gerresheimer Medical Systems plant in Germany in close collaboration with the Japanese partner. The first Gx RTF ClearJect product to be manufactured is the 1-ml long syringe with staked in needle. For more information, contact Gerresheimer at +49 211 6181 246 or visit **www.gerresheimer.com.**

Automated Delivery System

Insulet Corporation is an innovative medical device company based in Billerica, Massachusetts. Insulet designs and manufactures the OmniPod® Delivery System, an intelligent wearable subcutaneous pod used in a variety of therapeutic areas. This automated drug delivery system helps offer improved adherence, outcomes and differentiation throughout a drug's lifecycle. Equipped with a soft delivery cannula for a virtually painless experience and adhesive backing for extended wear, OmniPod is the on-body device that allows patients to live life uninterrupted. For more information, contact Insulet at (978) 600-7011or visit **www.omnipoddelivery.com**.

Highly Lubricious Material

Quniton™ has performance capabilities uniquely designed to improve and withstand Medical and Pharmaceutical application needs. Formulated to have a low coefficient of friction, it resists bonding or sticking to a wide range of materials and diversifying interface capability. Enhancing product lifespan, Quniton™ possesses non-reactive properties that ensure consistent surface-to-surface contact over time, retaining chemical and thermal stability. Industry applications include: MEDICAL & PHARMA - Plunger and Caps, Valves, Pumps, Seals, Syringe Plugs, Vial Seals, Catheters, Connections, and Diaphragms. For more information, visit Minnesota Rubber at (952) 927-1400 or visit **www.mnrubber.com**.

Technology & Services Showcase

Drug Delivery Solutions

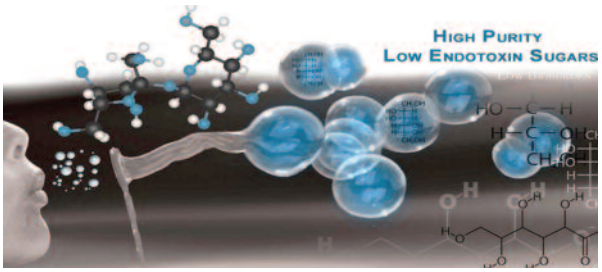
With over 1,500 people and 4 plants across two continents, **Nemera** is a world leader in the design, development and manufacturing of drug delivery solutions for the pharmaceutical, biotechnology, and generics industries. Nemera leverages decades of experience in the devices sector, from full solution development to pure contract manufacturing, through customized solutions. Nemera's expertise covers several modes of delivery: Ophthalmic (multidose, preservative-free eyedroppers), Nasal, Buccal, Auricular (pumps, valves, and actuators for sprays), Dermal & Transdermal (airless and atmospheric dispensers), Parenteral (auto-injectors, pens, safety devices, and implanters), and Pulmonary (pMDIs, DPIs). Over 5 million diabetics and 10 million asthmatics use every day the devices manufactured by Nemera. For more information, contact Nemera at information@nemera.net or visit **www.nemera.net**.

Device Training Platforms

noble®

Noble develops device-comparable injection and respiratory training platforms to provide biopharmaceutical companies improvements in patient medication adherence. These training platforms are built to brand specifications and are available as off-the-shelf and customized solutions, including proprietary technologies. Noble's offerings range from mechanical training devices to smart error-correcting training platforms, which replicate a brand's shape, design and tactile feedback, operational forces, and steps needed to administer the drug. These devices are designed to mimic actual delivery devices while being a low-cost reusable solution to safely and effectively onboard users. Benefits of patients using a device-comparable trainer before using an actual drug delivery device include users becoming familiar with a brand's device design, functionality, and ergonomics while learning correct administration technique. Companies providing reusable, device-comparable training products will be well positioned for competitive differentiation through improved patient satisfaction, adherence, and outcomes. For more information, contact Noble at (888) 933-5646 or visit **www.gonoble.com**.

Specialized Products & Services



Pfanstiehl is a leading cGMP manufacturer of parenteral grade excipients and highly potent APIs. Pfanstiehl develops and manufactures high-purity, low-endotoxin (HPLE) carbohydrates such as trehalose, sucrose, mannitol, galactose, and mannose utilized as injectable excipients for the stabilization of proteins, mAbs, and vaccines. These HPLEs are also used as supplements for industrial cell culture, cell therapy, and cryopreservation media. Pfanstiehl also works closely with some of world's largest multinational pharmaceutical and biopharmaceutical firms, as well as with virtual pharmaceutical companies, to synthesize proprietary and commercial compounds in quantities ranging from grams to MT quantities. Manufacturing and development occur at Pfanstiehl's a 13-building campus located near Chicago, IL. For more information, visit us at **www.pfanstiehl.com**.

Design, Development & Manufacturing

Phillips Medisize

Partnerships Built on Innovation

Phillips-Medisize is a global-leader in outsource design, development, and manufacturing services to the drug delivery, pharmaceutical, and medical device and diagnostics markets. We create satisfied customers by providing state-of-the-art technologies, innovative design, connected health solutions, and highly creative people with the skills to execute at a very high level on sophisticated projects. By partnering with our customers, early on, for device strategy and design through to manufacturing and supply chain, we assist with accelerating speed to market. We work with our customers to deploy advanced automated assembly and quality control technologies to reduce manufacturing cost while improving quality. It is our foundation and core principles – quality, innovation and investment – that have led us to our current industry position. For more information, visit Phillips-Medisize at **www.phillipsmedisize.com**.

Technology & Services Showcase

Room-Temperature Sterilization

REVOX® Sterilization uses a patented, room-temperature peracetic acid (PAA) vaporized sterilant that achieves exceptionally low chemical residuals and unsurpassed materials compatibility. With superior compatibility across a wider range of materials, engineers have more options to create products more efficiently. Companies can now create the products that will demonstrate their true potential. The REVOX™ technology eliminates inefficiencies associated with pre-conditioning and lengthy post sterilization wait times. This allows REVOX Sterilization to offer manufacturers a quick-turn, off-site sterilization service or cost efficient on-site, in-line processing. In May 2014, a Class II implantable device was granted FDA clearance with the REVOX sterilization process. The REVOX innovation is backed by a company with over 35 years of infection prevention and control advancements structured under strict regulatory compliance standards. For more information, visit REVOX at **www.revoxsterilization.com**.

Primary Containers

SiO2 Medical Products manufactures precision-molded primary drug containers molded from Cyclic Olefin Polymer (COP) and incorporates a thin, silicon-based barrier coating system on the inside surface. These primary containers combine the durability and dimensional consistency of plastic with the oxygen barrier properties, low extractables, and pH stability of a silicon-based coating. The containers have unique features not found in any containers on the market today and are ideally suited for sensitive, biopharmaceutical drugs. SiO2's on-line inspection systems deliver containers meeting a six-sigma quality level for critical defects, and each container has a unique ID for unparalleled track and trace capabilities. SiO2 Medical Products is based in Auburn, AL, with additional offices near Philadelphia, PA. For more information, contact SiO2 Medical Products at sio2-info@sio2med.com or visit **www.sio2med.com**.

Advanced Medical Technology

Terumo is one of the world's leading medical technology companies and operates in more than 160 nations. Terumo, founded in 1921, develops, manufactures and distributes a broad range of world-class medical devices including the supply of drug delivery/injection devices to the pharmaceutical industry. Terumo Pharmaceutical Solutions offers the pharmaceutical and biotechnology industry unique solutions in medical technology. In addition to offering our valued products, our specialized team also provides customized and dedicated solutions designed to meet your specific requirements. For more information, visit **www.terumo-ps.com**.

Integrated Delivery Systems

West is a leader in developing and manufacturing pharmaceutical delivery systems. The company has unique technologies in self-injection systems, including the SmartDose® electronic wearable injector and the SelfDose® injector, that enable patients to self-administer injectable medicines at home. West is also collaborating with HealthPrize Technologies on a connected health offering that is designed to improve and reward medication adherence with unique technologies. The offering integrates HealthPrize's Software-as-a-Service medication adherence and patient engagement platform into injectable drug delivery systems, providing biopharmaceutical companies and their patients with an end-to-end connected health solution. For more information, contact West at (800) 345-9800 or visit **www.westpharma.com**.

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TECHNOLOGY REPORT

Drug Platform Technologies

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drug-dev.com

External Delivery

International Business, Something to Consider

By: John A. Bermingham

John A. Bermingham is former Executive Vice President & COO of 1st Light Energy & Conservation Lighting, Inc. and former Co-President and COO of AgraTech, a biotech enterprise. He was also President & CEO of Cord Crafts, LLC; President & CEO of Alco Consumer Products, Inc., Lang Holdings, Inc., and President, Chairman, and CEO of Ampad, all of which he turned around and successfully sold. With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona, Corporation, and Rolodex Corporation as well as turning around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group, and President of the Magnetic Products Group, Sony Corporation of America.

Not every product, technology, or service is intended for international trade. But then again, not every business is intended to stay at home either.

So let's examine the possibility of expanding beyond the US borders.

Globalization and the reduction of foreign country trade barriers have vastly improved the ability of US businesses to expand internationally. There are several ways to achieve international business activity through what is called Foreign Direct Investment (FDI).

A company can make a greenfield investment, which is investing in a brand new facility, from the foundation on up. Or, a company could acquire an already established company in a foreign country through a merger or acquisition (M&A). There are pros and cons to both of these investment strategies, but most companies choose the M&A route.

Two other methods for international expansion are worth considering. Licensing and export. Licensing is when a company grants to another company the right to produce and market its products in the licensee's home for a royalty fee. The disadvantages are that the licensing company may have its technical expertise exposed, plus lose control over manufacturing, sales, and marketing. So protecting your company assets is paramount. Exporting may be considered if you produce a product but transportation costs may be so high that you will never make a profit.

Let's assume then that your company is not in a position to build a company from the ground up in a foreign country, acquire a foreign company, license a foreign company, or export its products to a foreign company.

What to do when you do not have the assets to realize one of the aforementioned strategies?

We solved that problem in one of the companies that I worked with.

It was a matter of our finding a partner in one of the foreign countries that we had targeted for our business. Because we were targeting multiple countries, we identified one primary partner, and together, we identified multiple "sub-partners" in the other countries that we had targeted.

We ended up with a large distributor in the Netherlands who covered not only their own country, but France, Italy, Germany, Belgium, Austria, and the UK. We had quarterly meetings in their office discussing strategy, quarterly performance, new products, local country product design and marketing issues, and competition.

Obviously, you need the Managing Director of the distributor to speak fluent English and have sales people and administrative people who speak acceptable English. So when you believe that, for various reasons, you should begin expansion into the international market, don't try to go it alone. While the process is not super hard, it can be tricky. Your distributor can help you a great deal in this area as ours did in setting up our business. We established both a business partnership and a personal partnership right away. We had the normal bumps in the road along the way, but it proved out to be a great business situation for both of us. ◆

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