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

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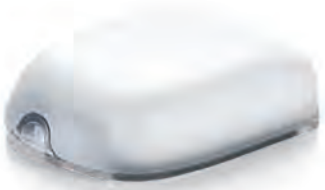

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Navigating Solubilization

"In particular, it is clear that a number of approaches have been successfully employed to deliver DCS class IIb compounds. So, the question still exists as to what technology should be selected for a new compound with poor bioavailability in its crystalline form. The goal of this 3-part series of The Second Quadrant is to add to our collective understanding of which specific solubilization technologies have achieved the best results in the past and those that offer the greatest promise today and going forward."

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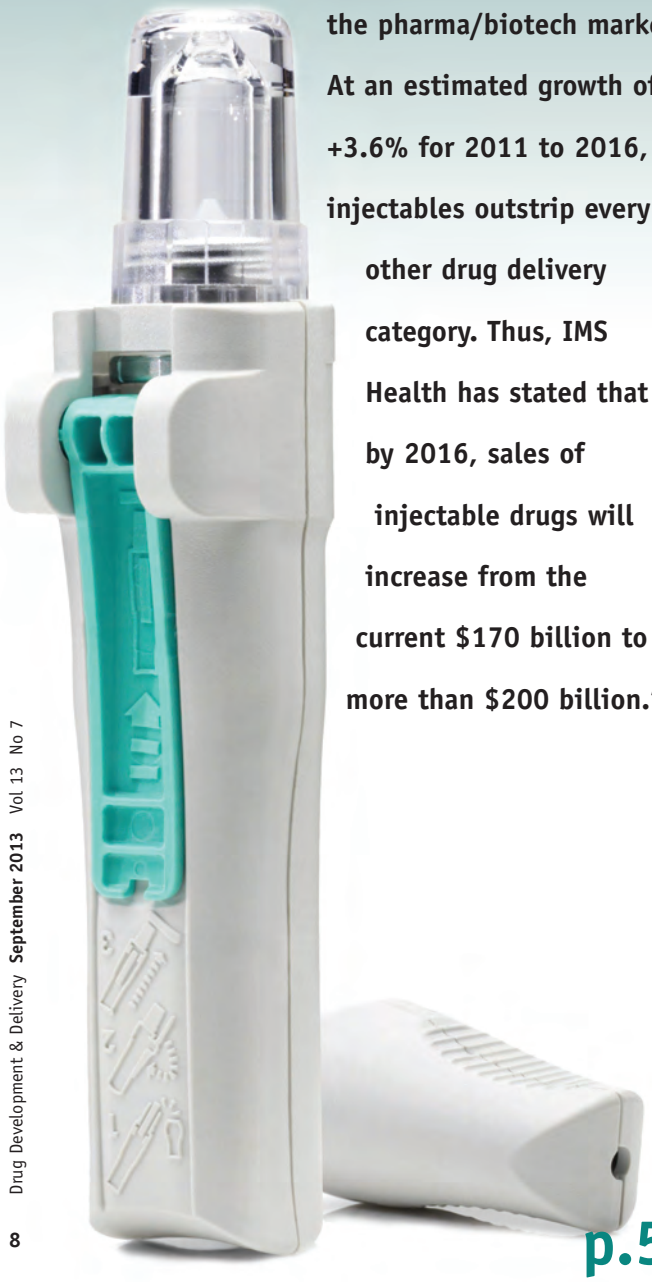
Hand Held Injection's Current Impact

"One of the most significant trends today in the drug delivery industry is the ascendency of the injectable market. According to information reported by Datamonitor in 2012, injectables as a whole (including those delivered by hand held devices) are becoming the single largest driver of the pharma/biotech market. At an estimated growth of +3.6% for 2011 to 2016, injectables outstrip every other drug delivery category. Thus, IMS Health has stated that by 2016, sales of injectable drugs will increase from the current $170 billion to more than $200 billion."



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Atlantic Pharmaceuticals Announces Successful Pre-IND Meeting for Abuse-Deterrent Hydrocodone

Atlantic Pharmaceuticals, Inc. recently announced it has completed a successful Pre-Investigational New Drug Meeting with the FDA on a single-component, immediate - release, abuse-deterrent hydrocodone (ATLP-03). Currently, all marketed prescription products containing hydrocodone also contain additional APIs that may be unnecessary or detrimental to the patients taking those products. Hydrocodone is also considered a drug with a high abuse potential, and current combination products can be crushed and administered nasally, injected, or chewed in order to obtain a rapid euphoria. In contrast to the currently marketed hydrocodone combination products, ATLP-03 does not contain any additional active ingredients and is formulated with Atlantic's patented abuse-deterrent SMART/Script system. ATLP-03 may be pursued under the FDA's abbreviated 505(b)2 NDA program in accordance with the outcome of the Pre-IND meeting with the FDA.

Atlantic's abuse deterrent platform, SMART/Script, has been designed to resist attempts to easily extract a drug from an oral dosage form and has the ability to sequester and reduce the drug release from a dosage that has been subjected to a variety of physical methods of tampering and abuse. The technology can be applied to immediate as well as sustained-release drug candidates.

SMART/Script (SMART, Simple, controllable, resistant, insoluble, physical trap), a novel, patented drug delivery technology, was designed to prevent easy drug extraction and to deter the abuse of medications via known routes of abuse or misuse, including chewing, snorting, and injecting. Orally delivered prescription pharmaceuticals, such as narcotics, are frequently subjected to abuse and misuse via chewing and swallowing or crushing and either snorting or injecting the resultant powder in order to obtain a fast euphoria. A product formulated with SMART/Script, however, resists extraction in water or alcohol and can be used with a broad range of opioids and non-opioids in immediate or extended-release forms. SMART/Script is also unique among competitive technologies in that physical manipulation, such as chewing or crushing, may result in reducing the release of the drug as opposed to increasing it.

Adimab Partners With Celgene Corporation

Adimab, LLC recently announced a multi-target discovery collaboration with Celgene Corporation of Summit, NJ. Under terms of the agreement, Adimab will use its proprietary platform to generate therapeutic antibodies against multiple targets. Celgene will have the right to develop and commercialize all therapeutic antibodies resulting from the collaboration.

"We are very pleased to announce another major pharma partnership," said Tillman Gerngross, CEO and Co-founder of Adimab. "Celgene has developed a highly successful oncology and inflammation franchise, and we are excited to partner with them to support their expanding antibody-based therapeutic portfolio."

Adimab and Celgene have entered into a collaboration whereby Adimab will use its proprietary discovery and optimization platform to identify fully human antibodies against multiple targets. For each target, the agreement grants Celgene the right to research antibodies generated during the collaboration for potential use as therapeutic products. Under the terms of the agreement, Adimab will receive an undisclosed upfront payment. In addition, for each target, Celgene will have the option to exclusively license antibodies generated during the collaboration. If Celgene exercises its option for a particular target, Adimab would receive license fees, clinical milestones, and royalties on therapeutic product sales.

"The speed and technical superiority of our platform drives all of our deal flow," said Guy Van Meter, Vice President of Business Development at Adimab. "The Adimab Platform is an extremely versatile antibody discovery and engineering tool that can be applied to a variety of different therapeutic development approaches, including IgG discovery, optimization, humanization, and bispecifics."

Over the past 4 years, Adimab has established collaborations with multiple leading pharmaceutical companies, including Merck, Roche, Novartis, Eli Lilly, Genentech, Biogen Idec, Novo Nordisk, Gilead, Kyowa Hakko Kirin, and GSK.

Adimab's integrated antibody discovery and optimization platform provides unprecedented speed from antigen to purified, full-length human IgGs. Adimab offers fundamental advantages by delivering diverse panels of therapeutically relevant antibodies that meet the most aggressive standards for affinity, epitope coverage, species cross-reactivity, and developability. Adimab enables its partners to rapidly expand their biologics pipelines through a broad spectrum of technology access arrangements.

New Syringe Designed to Position More Large-Volume Injectable Drugs for Prefill Administration

BD Medical recently announced the launch of BD Sterifill Advance, a new prefillable polymer syringe specially engineered to deliver large-volume injectable drugs by way of intravenous infusion.

BD Sterifill Advance is a 50-mL plastic prefillable syringe made with a highly advanced cyclic olefin polymer designed to offer a number of advantages to drug manufacturers and healthcare professionals, including reduced breakage, glass-like transparency, and low levels of extractables. This unique polymer combined with a specific coating technology provides smooth gliding, ensuring an accurate and consistent infusion rate.

"BD applied our extensive knowledge and experience with prefillable syringes to design this new syringe with properties that support the delivery of large-volume injectable drugs, making the advantages of this option more widely available," said Claude Dartiguelongue, President, BD Medical - Pharmaceutical Systems. "We are offering drug developers, healthcare workers, and patients a new option for prefill drug delivery that sets new standards in both safety and convenience."

The BD Sterifill Advance Plastic Prefillable Syringe aims to provide a seamless transition for healthcare workers in the hospital setting because the syringe was developed from the design of BD Plastipak, a leading disposable syringe. This unique design avoids any syringe pump reprogramming activity for hospitals and aims to reduce risks of administration errors for healthcare workers. In addition, the syringe has been designed to be highly durable, reducing the probability of flange breakage, and ensures a reliable connection with syringe pumps.

The syringe can address a number of drug delivery needs for the intravenous infusion of large volumes of drugs, including anesthesia, pain management, cardiac therapy, and nutrition amongst others. The product can also be used in a variety of settings for parenteral administration of pharmaceutical compounds.

Foamix Celebrates Receiving 20th US Patent

Foamix Ltd. recently announced the United States Patent and Trademark Office has granted US Patent No. 8,512,718, Pharmaceutical Composition For Topical Application, describing, inter alia, unique Oil-Gel compositions, which can be used in combination with therapeutic agents. These compositions, which primarily comprise hydrophobic solvents, are suitable for the delivery of a broad range of pharmaceutical agents targeting various diseases and disorders of the skin and the eye.

"We are delighted to have reached this landmark of 20 issued US patents, which is a major achievement and a reflection of the excellent work by Foamix's dedicated professional patent team and our proactive policy to provide intellectual property protection for Foamix's platform technologies and pharmaceutical product pipeline," said Dr. Dov Tamarkin, Foamix's CEO.

As a technology leader, Foamix collaborates with multinational and local pharmaceutical companies in the development of unique topical products. Foamix's versatile patent-protected OilGel and foam platforms enable the development of topical drugs with greater efficacy, favorable safety, and higher convenience profiles.

Foamix Ltd. is a clinical-stage, privately held specialty pharmaceutical company focused on the development of proprietary topical foams and OilGel products for dermatology, gynecology, as well as ophthalmic disorders. The company's lead product, Minocycline Foam, is the first-ever topical minocycline that can be used for the treatment of acne, rosacea, and skin infections. Foamix's current Phase II study has shown its Minocycline Foam to be a safe and effective topical treatment and an alternative to oral antibiotics, with superior efficacy and no significant side effects.

Minocycline, a well-known broad-spectrum antibiotic, is taken mainly for the treatment of acne, available only in oral dosage form. Foamix believes that a topical Minocycline foam could capture a significant portion of the oral anti-acne and anti-rosacea drug market, currently worth over $1 billion per annum, as it offers high efficacy with a favorable safety profile.

Pfizer's Lung Cancer Drug Rejected; Deemed Too Costly

Pfizer Ltd has expressed concern and disappointment that the final appraisal determination (FAD) from the National Institute of Health and Care Excellence (NICE) does not recommend Xalkori (crizotinib) for previously treated, ALK positive advanced non-small cell lung cancer (NSCLC). Whilst NICE has acknowledged that crizotinib may offer eligible patients better outcomes compared to standard chemotherapy, it has not been recommended for use within the NHS because NICE does not consider it to be cost- effective.

Pfizer is concerned about the impact this decision will have on eligible patients with previously treated NSCLC, whose tumors have been identified as ALK positive. As a personalized medicine, crizotinib allows targeted treatment of a specific group of patients who are most likely to benefit. In reality, the UK's limited and slow-paced adoption of innovative medicines such as crizotinib poses a real threat to both the government's goal to have UK cancer outcomes among the highest in Europe and its vision to make the UK a world leader in life sciences.

"As someone who cares for lung cancer patients on a regular basis, I am personally very saddened by this decision," said Dr. Michael Peake, Clinical Lead, National Cancer Intelligence Network and Consultant Physician, University Hospitals of Leicester. "Advanced lung cancer is an aggressive disease with very poor outcomes for many patients. Clinicians recognize the urgent need for personalized medicines that target the specific drivers of an individual patient's tumor. However, if patients are unable to routinely access such therapies, it leaves them at risk of potentially poorer outcomes than patients in other countries where they have access to personalised medicine."

Pfizer believes that the health technology assessment system makes it increasingly difficult for innovative medicines to be accepted for use within the NHS and available for the benefit of patients. During the appraisal process, NICE accepted that crizotinib offered patients a "noteworthy" improvement in progression-free survival and the number of patients responding to treatment was "very high" for a second or later line therapy in this difficult-to-treat cancer. Furthermore, NICE acknowledged that crizotinib was likely to extend patients' lives, but it was uncertain for how long. This was due, in part, to uncertainty in estimating the magnitude of overall survival benefit attributed to crizotinib.

Like many clinical trials for oncology medicines, the crizotinib trial was designed, for ethical reasons, to give patients allocated chemotherapy the opportunity to receive crizotinib once their cancer had progressed. This factor makes it difficult to compare the differences in overall survival between the two arms of the trial, because the majority of patients will have received crizotinib.

Following NICE's decision not to recommend crizotinib, the only other route for patients with previously treated, ALK positive advanced NSCLC to access the treatment is through the National Cancer Drugs Fund (CDF). However the CDF is only available to patients in England, treatments are not guaranteed to stay on it, and the future of its existence remains unknown. As such, a NICE recommendation still remains the optimal way to ensure all eligible patients in England and Wales have routine access to a second-line therapy. In addition, approval by NICE may improve the uptake of diagnostic testing, a necessary step in the treatment pathway for many targeted medicines.

Dr. David Montgomery, Medical Director, Pfizer Oncology UK, said, "The government's strategy for personalised care in cancer includes treating people with medicines targeted at the specific characteristics of their cancer. Yet crizotinib has not been well served by the current assessment models employed by NICE. Today's decision is another example of NICE declining a medicine, which we strongly believe is a clinically and cost-effective treatment. If this trend of negative decisions continues, we could see the UK fall even further behind other European countries for cancer survival rates."

InSite Vision Announces Patent Issuance on Ophthalmic Delivery System

InSite Vision Incorporated recently announced the United States Patent and Trademark Office (USPTO) has issued US Patent No. 8,501,800 on the company's DuraSite 2 next-generation enhanced drug delivery system. DuraSite 2 provides a broad platform for developing topically delivered ocular drugs with enhanced tissue penetration in order to improve efficacy and dosing convenience. This patent will provide utility/composition of matter protection to 2029 for both the delivery system and the drugs that are formulated with DuraSite 2.

"DuraSite 2 has the potential to significantly increase efficacy and reduce dosing requirements for topically delivered ophthalmic drugs. Based on its ability to significantly improve drug retention and penetration into the tissues of the eye, we believe DuraSite 2 could serve as a standard drug delivery technology across ophthalmic therapeutics," said Timothy Ruane, CEO of InSite Vision. "We plan to utilize the DuraSite 2 platform in the development of all future InSite Vision pipeline products and seek partners via licensing agreements."

In a large-scale, preclinical comparative study, a drug formulated with DuraSite 2 demonstrated significantly enhanced retention on the eye and tissue penetration as compared to the same product alone or formulated with InSite Vision's DuraSite technology. Results of that study showed that the DuraSite 2 formulation achieved more than 2x and 4x concentrations in the aqueous humor of the eye as compared to the DuraSite formulation or marketed drug, respectively. The robust results of this study suggests that DuraSite 2's increased tissue penetration may enable it to be used in the treatment of back-of-the-eye diseases with a topical eye drop when formulated with drugs that must currently be administered by injection.

While eye drops are a proven delivery mechanism for numerous ocular drugs, the efficacy of these agents is impeded by tears and blinking, which rinse the drug from the surface of the eye and limit retention and absorption. InSite Vision's DuraSite and DuraSite 2 platforms are sustained delivery technologies using a synthetic polymer-based formulation designed to extend the residence time of a drug relative to conventional topical therapies. DuraSite and DuraSite 2 enable topical delivery of a solution, gel, or suspension and can be customized for delivering a wide variety of potential drug candidates. The DuraSite platform is currently leveraged in two commercial products for the treatment of bacterial eye infections, AzaSite and Besivance.

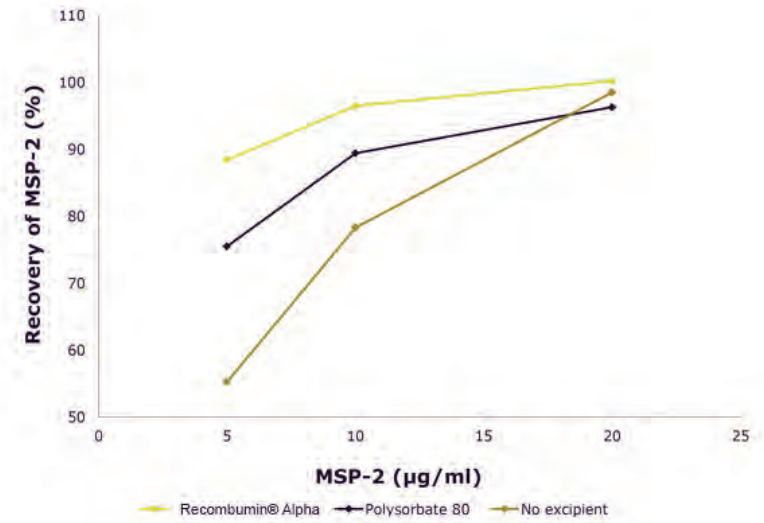
Maximizing the Stability of Therapeutic Proteins Using Recombinant Human Albumin

By: Mark Perkins, PhD

The year 2012 was a good year for the industry, with a record 39 NMEs (New Molecular Entities) approved by the FDA. However, many experts believe this headline figure masks continuing issues with pipeline and productivity. Phase II clinical trial success rate for experimental drugs was just 22% for the 5-year period ending in 2011. Phase III was better, but still decreased to 65% from 70%. At the same time, the number of preclinical programs needed to produce a single new drug increased from 12 to 30.[1] Pressure is therefore increasing for companies to pursue molecules with challenging profiles for further development. This is particularly true for many biological drugs in which a complex range of factors contribute to the stability profile of the molecule. A detailed understanding of these factors and the ability to control them is

FIGURE 1A & 1B

A



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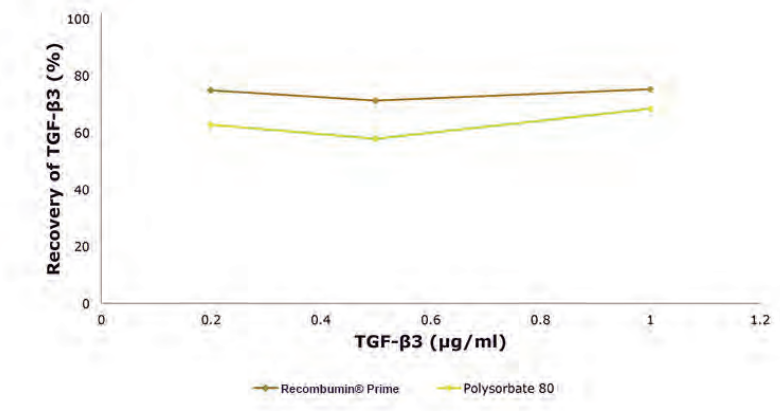

Protein recovery of HSP-2 and TCF-β3 following incubation with rAlbumin, polysorbate 80, and no excipient.

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The challenges of formulating a therapeutic protein are many, including a susceptibility to aggregation, oxidation, and surface adsorption; a particular challenge when formulating at extremely low doses. As the percentage of aggregation, oxidation, and surface adsorption in a formulation increases, the efficiency of the product decreases. In summary, formulators face real challenges in taking a protein and turning it into a viable therapeutic for the marketplace. In this article, we review some of the important factors involved, and highlight the advantages of including recombinant human albumin to stabilize protein therapeutics with reference to a recent case study.

STABILIZING PROTEIN DRUG FORMULATIONS

In order to stabilize, and therefore increase efficiency of protein drugs, formulators should aim to control aggregation, oxidation, and surface adsorption in their final products, among other factors. Two common techniques are used to achieve this. First, genetically engineering and altering the substance sequence with the help of detailed predictable algorithms and technologies. This can be an efficient solution, although such algorithms are not always available for the prediction of more complex small molecules, macromolecules, and peptides, all of which are becoming more and more common in today's therapeutics.[2]

Optimizing the drug formulation by adding stabilizing excipients also provides a solution. However, many methods for stabilization require multiple excipients, such as human serum albumin (HSA), a variety of sugars, amino acids, and detergents (SADs).

HUMAN SERUM ALBUMIN

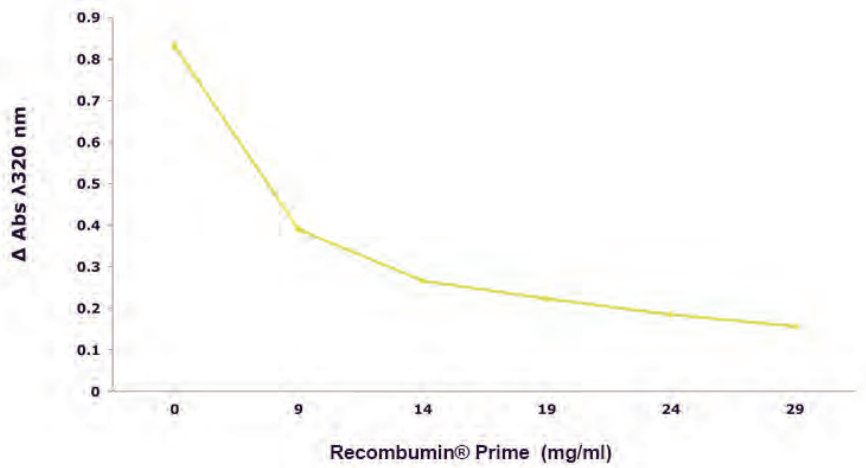
HSA is the most common protein found in human plasma and is known for its ligand binding and contribution to the colloidal stability of the blood. The physical properties that allow albumin to carry out its biological function also make it the perfect stabilizer for many biological drugs, particularly in liquid formulations. In addition, the abundance and natural self-tolerance to albumin minimizes the likelihood of HSA eliciting an immune response in a given patient population.

The study discussed further explores the ability of two recombinant human albumins (rAlbumin) from Novozymes Biopharma to prevent and protect against surface adsorption, aggregation, and oxidation.

PROTECTION AGAINST SURFACE ADSORPTION

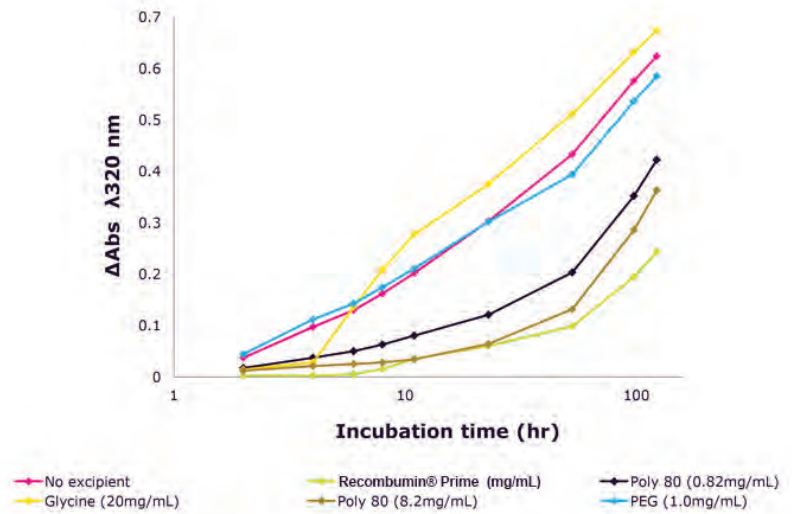
The binding of protein molecules to exposed surfaces can be a real issue for formulation scientists working with high-potency/low-dose drugs. Most proteins

FIGURE 2



Fibril formation in MSP-2 antigen with exposure to varying concentrations of r-Albumin.

FIGURE 3



Fibril formation in MSP-2 antigen with exposure to various commonly used excipients.

will adsorb non-specifically to primary packaging materials, such as glass vials leading to a significant reduction in available dose. Formulators can engineer these issues out of their final products by adding blocking agents to limit non-specific adsorption.

Albumin's high interfacial activity means it has the ability to prevent protein adsorption in low-dose formulations.[4] To investigate the potential of Recombumin Alpha and Recombumin® Prime (Recombumin®) as a blocking agent, percentage protein recovery was measured following exposure to glass vials of either transforming growth factor β (TGF-β), often used in scarless wound healing, and merozoite surface protein 2 (MSP-2), the malarial vaccine antigen. Throughout the course of the investigation, Recombumin® was incubated at room temperature in a glass vial for 20 minutes in the presence of a phosphate buffer and either TGF-β or MSP-2. Protein recovery was then measured by reverse phase high performance liquid chromatography. As a comparison, the same method was followed using polysorbate 80, a widely used blocking agent in the formulation of protein products.

As shown in Figure 1, Recombumin® was the most effective agent in preventing non-specific binding to glass for both MSP-2 and TGF-β, causing significant reductions when exposed to the latter. Compared to polysorbate 80, Recombumin® was shown to reduce product loss to a greater extent in both cases. In the complete absence of a blocking agent, no TGF-β was recovered (not shown).

AGGREGATION INHIBITION

With huge potential for loss, reduced efficiency, and increased product immunogenicity, protein aggregation during product storage is a major concern for formulation scientists. With FDA focus increasingly on regulating the number and size of particles present in formulations, it is important that formulators can control and reduce these numbers. This challenge particularly affects protein products formulated at

SIDEBAR

ABOUT RECOMBINANT HUMAN ALBUMIN

Manufactured specifically for the biopharmaceutical and medical device markets, especially when dealing with difficult-to-stabilize formulations and proteins, Novozymes Biopharma's animal-free, recombinant human albumins (Recombumin®) are applicable in formulation, drug delivery, and medical device coating. Proven to stabilize proteins by preventing aggregation, oxidation, or adsorption of the active drug, Novozymes' Recombumin® are pure, high-quality ingredients that can help customers deliver safer products to the market faster. Recombumin® Alpha is supplied as an ingredient for the manufacture of pharmaceutical drugs, medical devices, and advanced cell therapy products. Approved for use in the manufacture of human therapeutics, Recombumin® Prime is the world's first commercially available, GMP-manufactured, animal-free rAlbumin developed for drug and vaccine manufacturing. Novozymes' rAlbumins are manufactured to regulatory standards to deliver a secure supply of batch-to-batch consistency and increased efficiency for customers looking for a compliant albumin alternative.

high concentrations, as aggregation can be concentration dependant. HSA is an effective inhibitor of Aβ fibrillization, having been shown to bind to Aβ oligomers that are competing with Aβ monomers, preventing the growth of oligomers into larger assemblies.[5]

While evaluating Recombumin®'s ability to suppress fibrillization, MSP-2 was exposed to a freeze-thaw cycle known to induce fibril formation. This was repeated in the presence of various concentrations of Recombumin® dissolved in the buffer solution. After a single freeze-thaw cycle, the presence of fibrils was measured by the absorbance at 320 nm using RP-HPLC. When complete, results showed that the inclusion of Recombumin® noticeably reduced amyloid formation (Figure 2).

Using the same experimental model, commonly used excipients were tested and compared to Recombumin®. The other commercially available excipients tested were glycine, PEG 400, and polysorbate 80. In all cases, Recombumin® was shown to suppress aggregation of the MSP-3 antigen to a greater extent (Figure 3).

ANTIOXIDANT PROPERTIES

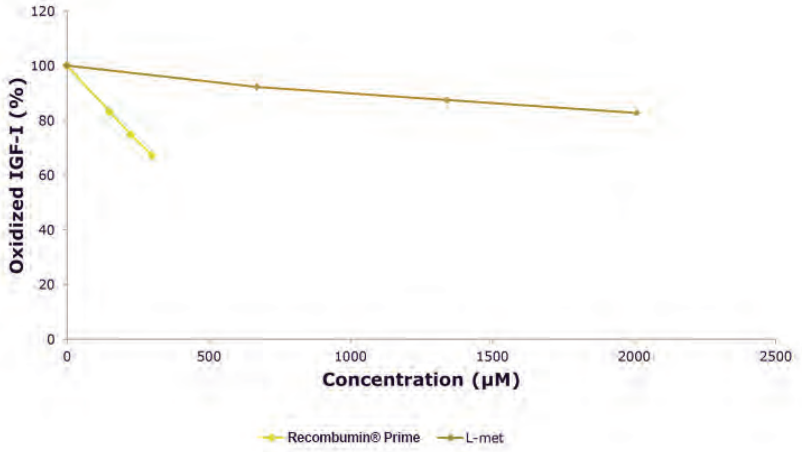
Oxidation of a protein drug product can lead to a range of functional changes, including altered binding activities, increased susceptibility to aggregation and proteolysis, increased or decreased uptake by cells, and altered immunogenicity. Oxygen (headspace), light, temperature, and the product's physical state can all affect the rate by which oxidation occurs.

HSA has been proven to have an antioxidant function, due to both the single free thiol at position Cys 34 and to surface-located methionines. These act as scavengers for reactive oxygen and nitrogen species.[6]

To test the functionality of Recombumin® as an antioxidant, relevant conditions for protein oxidation were modelled using trace amount of the oxidizing agent hydrogen peroxide (H_2O_2). Recombumin® was dissolved in a

FIGURE 4A & 4B

A



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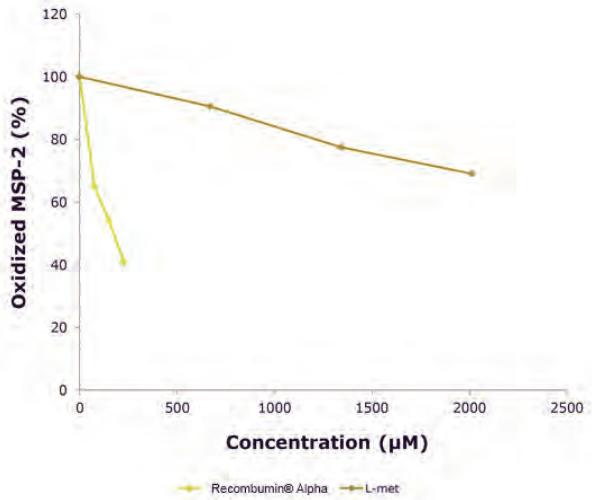

Percentage of oxidized protein products in the presence of rAlbumin and L-methionine.

buffer solution, and the protein products IGF-I protein (20 µg/ml) or MSP-2 (40 µg/ml) were then added to all samples, followed by peroxide treatment. The reaction was terminated with catalase, and the percentage oxidized measured by RP-HPLC. The same method was then followed using L-methionine as a comparison.

Figure 4 shows that the presence of increasingly concentrated Recombumin® significantly reduced oxidation of IGF-I or MSP-2. It was also shown that the oxidative protection of both protein products by Recombumin® was achieved at molar concentrations ten-fold less than that of L-methionine.

SUMMARY & CONCLUSION

The study presented here demonstrates that Recombumin® is an effective multipurpose excipient, with the ability to protect protein products from aggregation, non-specific adsorption, and oxidation. The use of Recombumin® enables formulation scientists to simplify their strategies and reduce the number of excipients needed to stabilize a protein drug or vaccination candidate. As a result, less time is spent refining combinations of excipients, reducing production times, and promoting the creation of drug formulations that are more reliable for both manufacturers and patients. ◆

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BIOGRAPHY

Dr. Mark Perkins is a Formulation Chemist with a PhD in Pharmaceutical Sciences from the University of Nottingham. As Customer Solution Manager, Dr. Perkins works with partners who are evaluating Novozymes Biopharma's recombinant albumin products and associated technologies in the areas of biopharmaceutical formulation and half-life extension. Prior to this position, Dr. Perkins worked as a Materials Specialist at an inhaled drug development company and as a Project Manager within an analytical consultancy. He can be reached at mrpk@novozymes.com.

Nanocomposites for Drug Delivery Catheters

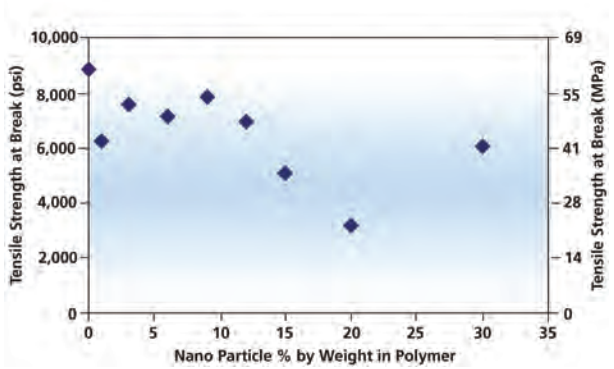
By: Lawrence A. Acquarulo Jr., PhD

After more than a decade of evaluation in medical devices, nanoparticle-reinforced polymers are increasingly being sought out for tailoring performance characteristics of vascular catheter shafts.[1] Reinforcing nanoparticles affect the polymer at the molecular level to improve transmission performance properties (ie, pushability and torque) for advancing these devices into more distal regions of the body, without affecting surface smoothness, flexibility, or radiopacity of the shaft.

Neurological microcatheters with diameters less than 0.03 inches (0.7 mm) are able to reach regions of the brain from a femoral artery access. These devices create new paradigms for diagnostics, surgical procedures, and local drug delivery. Traditional polymers used for construction of shorter shafts with larger diameters are not always suitable for such devices.

Despite smaller diameters, thinner wall sections, and longer shafts used for advanced microcatheters, the properties required to advance and navigate the catheter to the distal site remain. Pushability without buckling, flexibility without kinking, and responsiveness of the distal end to applied torque at the proximal end for navigation (ie, torque transmission) are desirable characteristics of catheter shafts.

FIGURE 1



Nanoparticle Effect on Tensile Strength of PEBA Polymer with 72 Durometer Hardness

CATHETER SHAFT PERFORMANCE

Two common characteristics of catheter shaft performance include pushability and flexibility. Pushability refers to the forward force applied by a physician to advance the catheter toward the designated therapeutic site, against which resistance is encountered from movement through non-linear vascular pathways.

The section of catheter between the physician's hand (proximal end) and the patient's vascular access may be theoretically assessed as an engineering column. Thus, column buckling equations may be used because the physician must be able to apply sufficient pressure to overcome vascular resistance on the leading portion inside the body (distal end), without the portion outside the body collapsing. Because the vascular pathway is non-linear, the catheter must remain flexible enough to navigate the bends without causing trauma to the patient or undue friction during insertion. Flexibility can be predicted by rigidity equations of the tube.

A desirable catheter shaft may include one with sufficient buckling strength to fully insert the catheter into the therapeutic site, while having the least amount of rigidity to navigate the desired vascular pathways without causing trauma to the patient.

The common material characteristic used in predicting buckling and rigidity is elastic modulus. For a shaft with a uniform cross-section along the length, a material with a high elastic modulus will have a greater resistance to column buckling under load, and will therefore improve pushability, yet increase rigidity of the shaft for navigation. Selection of a material with the precise elastic modulus is necessary to provide the ideal balance between pushability and flexibility for a given shaft construction.

MATERIAL LIMITATIONS

Polymers are key building blocks in catheters. Polyamides, polyether block amides (PEBA), and thermoplastic polyurethanes (TPU) are preferred for most applications due to their biocompatibility and mechanical properties. Within these classes are a number of polymer types, grades, and suppliers that provide a range of performance properties, including elastic moduli. However, gaps remain in the availability of precise properties.

Enhancing the elastic modulus of polymers for non-medical applications is often achieved by adding glass, carbon, and other fibrous materials to the polymer. These fillers are far too large in size for the extrusion of extremely thin wall catheters with smooth surfaces.

Reducing fiber lengths of these traditional fillers to accommodate thin sections has had limited success. The critical factor in the success of polymer reinforcement is the aspect ratio (or length-to-thickness ratio). Additives with aspect ratios of less than 20:1 do not generally provide meaningful strength enhancements to be considered reinforcing agents. Thus, reduction in traditional fiber size through length reduction alone is insufficient.

When reinforcing agents are reduced substantially in both length and diameter, there is often an agglomeration between the small particles, and thus difficulty dispersing the filler in the polymer melts. Poor dispersion of the reinforcement can create unpredictable and often deficient performance in the finished part.

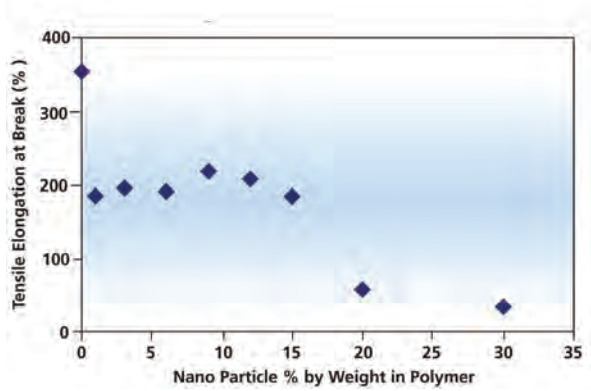
NANOPARTICLE OPTIONS

Nanocomposites were first referenced as early as 1950, and polyamide nanocomposites were reported as early as 1976. However, it wasn't until Toyota research labs began working with polymer-layered silicate clay mineral composites in the early 1990s that nanocomposites became more widely studied.

Today, there are a variety of nanofillers for use in nanocomposites. However, due to cost and availability, a great deal of focus is currently on nanoclay particle reinforcements in plastics. These reinforcements are slightly more expensive than glass, yet generally much less expensive than carbon reinforcements. Additionally, the low amount of nanofillers required to enhance properties allows for these nanocomposites to more effectively compete with traditional glass fiber reinforcements.

Nanoclays are minerals that have high aspect ratios and with at least one dimension of the particle in the nanometer range. Reinforcements in the nanometer size range closely approach the molecular size of the polymer. This makes for a very intimate

FIGURE 2



Nanoparticle Effect on Tensile Elongation of PEBA Polymer with 72 Durometer Hardness

encounter between the two materials. When properly modified, the filler particles and polymer interact to create very constrained regions at the particle surface. This immobilizes a portion of the polymer chain creating a reinforcement effect.

Two characteristics of nanoclay particles that are critical to their success as polymer-reinforcing agents are purity and cation exchange capacity. Purity is important in achieving maximum increases in mechanical properties. Impurities act as stress concentrators, resulting in poor impact and tensile properties. Cation exchange capacity provides the surface activity necessary for acceptance of surface treatments to the clay. This treatment is essential to allow the small particles to be effectively accepted and dispersed in the polymer matrix.

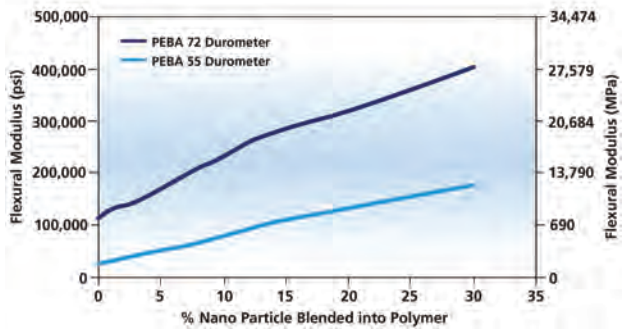
UNDERSTANDING NANOCLAY REINFORCEMENTS

The most important factor in evaluating nanoclay reinforcements is the aspect ratio of the clay particle. Clays that have a platy structure and a thickness of less than one nanometer are preferred. The length and width of the choice clays are in the micron range. Aspect ratios of the choice clays are in the 300:1 to 1,500:1 range.

Montmorillonite clays have had the widest acceptability for use in polymers. These are smectite clays that can absorb water and have a layered structure of aluminum octahedron sandwiched between two layers of silicon tetrahedron. Each layered sheet is slightly less than 1 nanometer or 10 angstroms thin with surface dimensions extending to about 1 micron or 1000 nanometers. This results in a surface area is in the range of 750 square meters per gram (228,717 sq ft/oz) of clay.

Because montmorillonite clay is hydrophilic, it is not inherently compatible with most polymers and must be chemically modified to make its surface more hydrophobic. The most widely used surface treatments are ammonium cations, which can be exchanged for

FIGURE 3



Nanoparticle Effect on Flexural Modulus of PEBA Polymer

existing cations already on the surface of the clay.[2] The treatments work on the clay to minimize the attractive forces between the agglomerated platelets.

This process of separating the nanoclay platelets is referred to as the intercalation process. Without this separation, the nanoclay is not capable of allowing the polymer to penetrate between the platelet layers.

In the exfoliated form, nanofillers have a flexible platelet type structure that is very small. The thickness of the platelet is in the nanometer range, while the length and width are in the tenth to 2-micron size. Because of this, it can be said that a single gram of exfoliated nanoclay will contain over a million individual particles.

NANOPARTICLE-REINFORCED POLYMERS

Nanoclays are melt-compounded into polymers using twin screw extrusion technology. The compounding parameters and mixing screw profile are important variables in combination with the pretreatment of the clay itself.[3] Because the clay is an aggregate of thousands of individual platelets, it is critical that the individual platelets be separated prior to compounding. If the platelets are not separated, it is unlikely that the shear forces generated during the compounding process will be great enough to overcome the forces holding the aggregates together. Hence, less-than-optimum exfoliation or dispersion will result.

Application of the right clay treatment is required to allow for intercalation and making the intercalate compatible with the host polymer so properties are enhanced without the sacrifice of other properties. This is what allows for improvement in the strength without making the polymer brittle. Secondly, melt-compounding must occur such that the prepared clays get maximum dispersion without degrading the polymer.

BENEFITS OF NANOPARTICLE-REINFORCED POLYMERS IN MEDICAL DEVICES

Polyamide 11 and 12 polymers, and PEBA copolymers are commonly used to manufacture vascular catheters, and have become the materials of choice for percutaneous transluminal coronary angioplasty (PTCA) applications that include balloon and stent delivery catheters.[4] These materials have proven to be sufficiently flexible to minimize trauma while navigating the vascular pathways, yet rigid enough for pushability and torque transmission to reach the desired site.

PEBA copolymers are considered thermoplastic elastomers based on polyamide 11 and 12 chemistry. These materials offer lower hardness and rigidity than polyamides, yet typically more rigidity than many thermoplastic urethanes. By varying the copolymer constituents, suppliers of PEBA are able to provide a range of grades with varying rigidity and hardness. Nanoclay particles can be added to these polymers to further tailor rigidity for specific catheter applications.

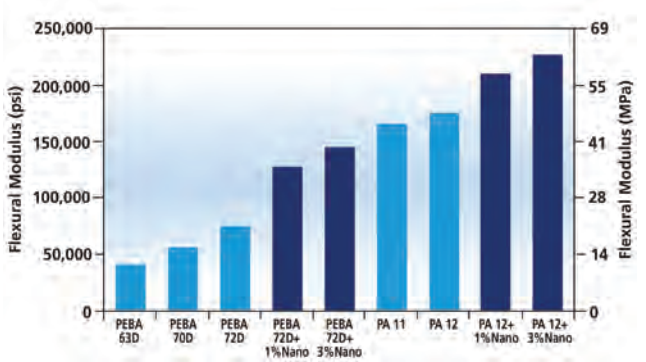
Nanoclay particles added to polymers commonly used in catheters primarily affect flexural properties. Often, other mechanical properties, such as tensile strength and elongation, remain relatively unaffected. As shown in Figure 1, tensile strength of a PEBA with a Shore Hardness of 72D is relatively unaffected in compounds with up to 12% by weight of nanoparticle reinforcements in the formulation.

Tensile elongation at break also remains high for the same polymer, after an initial drop that may be attributed to either the addition of any additive or the addition of heat and shear from extrusion compounding (Figure 2).

The mechanical property most affected by the addition of nanoparticles is flexural modulus (Figure 3). This property is directly related to rigidity of the shaft and therefore of primary consideration.

Thus, in low-to-moderate loadings, nanoparticles can improve flexural modulus of catheter polymers while maintaining relatively high levels of tensile properties. This provides the ability to tailor

FIGURE 4



Nanoparticle Reinforcements Extend Modulus Range of Traditional Polymers

pushability and flexibility for a desired catheter application.

This tailoring is most useful in bridging gaps in the available flexural moduli from unmodified polymers.[5] The most rigid, commercially available PEBA polymer has a 72 Shore D Hardness (72D) and flexural modulus of 74,400 psi (513 MPa). When greater stiffness is required, many design engineers consider polyamide 11 with a flexural modulus of 165,300 psi (1,140 MPa), more than twice that of 72D PEBA. Low concentrations of nanoparticles melt blended into the 72D PEBA can bridge the gap in ridigity between these two materials for tailoring pushability and flexibility of catheter shafts. Nanoparticles can also extend the flexural modulus properties of polyamides (Figure 4).

SUMMARY

Twin screw extrusion offers excellent dispersion of nano-size particles in polymers used for catheter shafts. This results in custom polymer blends with appearance, processing, and performance properties not dissimilar to unmodified polymers. For designers of minimally invasive devices, such as diagnostic, interventional, and drug delivery catheters, this provides a much broader portfolio of materials for tailoring device performance as compared to working only with commercially available, unmodified polymers. This increased availability of medical materials could create a new wave in the development of precision devices to reach smaller areas deeper within the body. ◆

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BIOGRAPHY

Dr. Lawrence A. Acquarulo, Jr. is the Founder and CEO of Foster Corporation, a developer and manufacturer of critical polymer compounds for medical devices and drug delivery. He earned his his Bachelors degree in Plastics Engineering from the University of Massachusetts Lowell, followed by a Masters degree in Material Science from The University of Connecticut, a PhD in Engineering Management from Kennedy Western University, and a CPD in Business Strategy from the Wharton School, University of Pennsylvania. Dr. Acquarulo has six US and international patents in the field of nanocomposites, cross-linkable polymers, and lubricated and drug-filled polymers for medical device and industrial use, and has published over a dozen technical papers in leading journals. Under his leadership, Foster Corporation has become a world leader in biomedical polymer compounding and recent recipient of the Deloitte Technology Fast 500 award and the Marcum Tech Top 40.

Next generation HPMC capsules greatly expand pharmaceutical uses

by Dominique Cadé, PhD

A powerful alternative for pharmaceutical dosage forms

Polymer choices in pharmaceutical dosage forms have always been a balancing act between performance and development time, and historically has been shaped by the interactions of gelatin. The first generation of HPMC capsules, which relied on a secondary gelling agent, were recognized by formulators as having issues with dissolution performance and product stability. Fortunately, new scientific discoveries in polymers and capsule manufacturing have resulted in the creation of the next generation of HPMC capsules – one that offers better performance and reduced development time compared to gelatin and first-generation HPMC capsules.

Capsugel, the market leader in research and development in this area, is now offering these second-generation HPMC capsules under the trade name, Vcaps® Plus capsules.

In a number of studies, Vcaps Plus capsules have been shown to deliver optimized compound stability and predictable *in vitro* dissolution while also helping to eliminate the complexity in formulation development. Known globally for their reliable and predictable performance, Vcaps Plus capsules are well suited for over-the-counter (OTC) or off-patent products as well as for new chemical entities (NCEs).

True pH and ionic media independent performance

Traditionally, HPMC capsules were created using secondary gelling agents and ionic gel promoters, which have been found to interact with dissolution media and delay compound release from the capsule. The activity of the gelling agent kappa-carrageenan, for example, is enhanced by potassium and calcium cations contained in many foods. The extent of the resulting delay in dissolution time was shown in an *in vitro* test in which caffeine-filled traditional HPMC capsules were dissolved in a number of dissolution media. In the simulated normal acidic environment of the stomach (pH 1.2 USP), 90% of the caffeine was dissolved within approximately 15 minutes (Figure 1). Adding 2 g/L of potassium chloride (KCl) to this medium resulted in no dissolution after 15 minutes and a caffeine dissolution between 70% and 80% after more than one hour. Increasing the KCl content to 9 g/L delayed caffeine release even further, with a dissolution rate of just over 10% in 45 minutes. Results with simulated milk fluid were equally disappointing. Similar delays in dissolution times were observed and attributed to carrageenan in an independent study (Ku et al., 2011). Of course, such long delays in capsule dissolution are unacceptable particularly for rapid-relief products.

Capsugel addressed this situation by developing a proprietary new thermal gelation manufacturing process for Vcaps Plus capsules that eliminates the need for gelling systems all together and provides true pH and ionic media independence in disintegration. *In vitro* tests showed that these second-generation HPMC capsules had similar rates of dissolution at pH levels of 1.2 and 6.8 and with simulated milk fluid, achieving a nearly complete dissolution of the caffeine contents within approximately 30 minutes (Figure 2). Even adding 2 g/L or 9 g/L of KCl to the dissolution medium did not affect the performance of Vcaps Plus capsules, with dissolution of over 90% within 30 minutes, even under the most disadvantageous condition.

These findings were supported by an independent study that compared the dissolution performance of traditional and second-generation HPMC capsules (Ku et al., 2011), and underscores the superior performance of Vcaps Plus capsules.

Ideally suited for moisture sensitive compounds

While gelatin capsules have been effectively used for over a hundred years, due to their excellent flexibility and highly desirable dissolution properties, they are not typically the polymer choice for moisture sensitive compounds. Vcaps Plus capsules on the other hand have a three-fold lower moisture content than gelatin capsules and are less hygroscopic. That equates to fewer broken capsules due to brittleness and less of a chance of drug degradation compared to gelatin capsules.

Figure 1

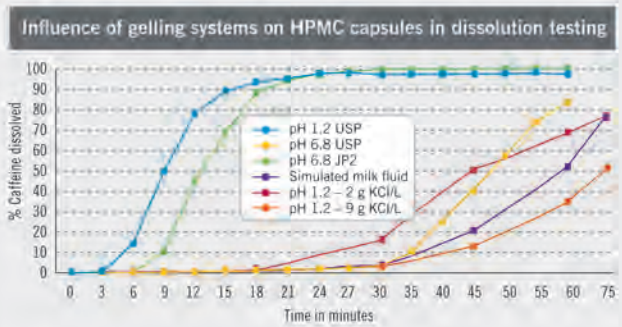
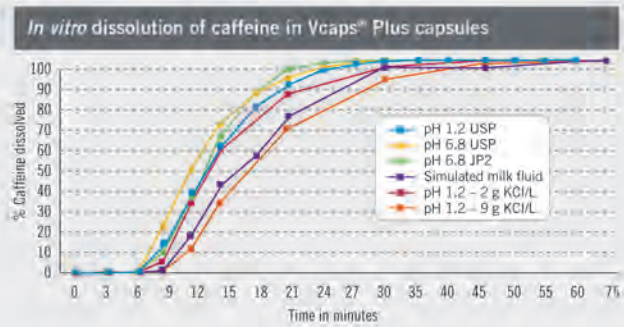


Figure 2



Improved stability at high and low temperatures

Capsugel in-house studies and an independent study conducted at Wyeth (Ku et al., 2010) have demonstrated the superior stability of Vcaps Plus capsules. An exposure of up to one week to temperatures ranging from 4°C to minus 18°C did not change the appearance or performance of unfilled Vcaps Plus capsules in closed high-density polyethylene (HDPE) bottles. The same stability was found with empty Vcaps Plus capsules in fully-filled glass bottles that were heated for 24 hours to temperatures ranging from 40°C to 60°C.

In long-term storage condition studies, including a 6-month storage at 40°C and 75% relative humidity and 2 years at either 25°C and 65% relative humidity or 30°C and 70% relative humidity, Vcaps Plus capsules disintegration and dissolution characteristics remained unchanged.

The wider temperature capabilities of Vcaps Plus capsules make them the perfect choice for longer term storage and when used in progressively unpredictable home environments.

Superior machinability

Traditional and second-generation HPMC capsule attributes have been compared on many common high-speed capsule filling machines (Ku et al., 2010). With respect to filling and rejection rates, Vcaps Plus capsules performed much like gelatin capsules and were superior to traditional HPMC products. In addition, Vcaps Plus capsules can be adapted for use with liquid compounds.

Wide regulatory and industry acceptance

Vcaps Plus capsules are manufactured in certified ISO 9001 facilities and in accordance with IPEC's (International Pharmaceutical Excipient Council) Good Manufacturing Practice (GMP) Guide for Bulk Pharmaceutical Excipients. They are acceptable for use in pharmaceutical and dietary supplement oral dosage applications in major markets of the US, Canada, EU, Japan, and Australia. In addition, Vcaps Plus capsules are certified Kosher Ko and Halal by IFANCA, and are approved for vegetarians by the Vegetarian Society.

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Vcaps® Plus

For more information about Vcaps® Plus capsules visit VcapsPlus.com.

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The Second Quadrant

Navigating a Broad Spectrum of Solubilization Technologies: Part I of III

By: Marshall Crew, PhD, President & CEO, Agere Pharmaceuticals, Inc.

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UBM

In the past two columns, *The Second Quadrant* focused on excipients and the roles they play in the quest to overcome bioavailability challenges of poorly soluble drugs. For the next three issues, we will hear perspectives of experts whose respective companies provide solubility-enhancement technologies to the industry. Various old and new technologies exist, most of which are represented by the participants in this column. The goal of this particular series is to provide information to assist in selecting appropriate solubilization technologies for different compounds.

For those with limited experience in the delivery of poorly soluble compounds, the selection of the ideal technology for a particular drug candidate can be daunting. Since the 1970s, many different approaches have been attempted and developed, and numerous reviews have been published. The BCS (Biopharmaceutical Classification System) was developed as a regulatory tool to give guidelines and recommend classification of drugs into four quadrants based on dosage form dissolution and the solubility and permeability characteristics of the drug substance. The addition of DCS (Developmental Classification System) further partitioned class II compounds based on dissolution rate and solubility, with the goal of assisting in the selection of appropriate delivery approaches for new drug candidates. An analysis by James Butler of GlaxoSmithKline features selected drugs and the respective solubilization technologies used in the four main quadrants of the DCS system (Figure 1).[1] This figure provides interesting insight into where the different technologies have historically been applied to achieve improved bioavailability. From this map, it can be seen that while particle size reduction has dominated for dissolution rate-limited drugs, a broader range of technology options is represented when addressing solubility-limited drugs. In particular, it is clear that a number of approaches have been successfully employed to deliver DCS class IIb compounds. So, the question still exists as to what technology should be selected for a new compound with poor bioavailability in its crystalline form.

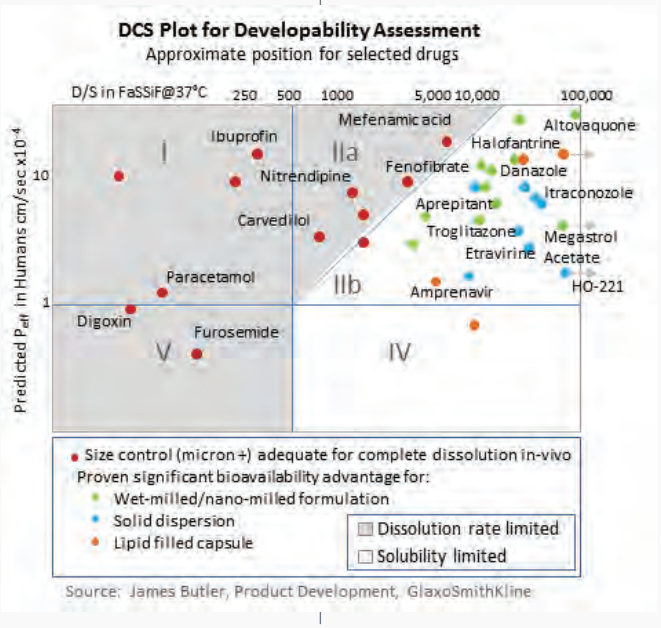
The goal of this 3-part series of *The Second Quadrant* is to add to our collective understanding of which specific solubilization technologies have achieved the best results in the past and which offer the greatest promise today and going forward. To help readers better navigate the available options, representatives of a broad range of technologies provide their views on a number of questions important to those considering different approaches for a poorly soluble compound.

"…the dose-to-solubility ratio is a key indicator of the solubility challenge that a given compound presents."

Tom Dürig,
Senior R&D Director - Pharmaceutical & Nutrition Specialties,
Ashland Specialty Ingredients -
tdurig@ashland.com

The companies represented include those offering lipid-based solubilization, amorphous solid dispersions, particle size reduction, particle engineering, nanoparticles, and co-crystallization. I am grateful for the efforts of each of the contributors and their thoughtful responses.

FIGURE 1



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SELECTION CRITERIA

Q: What API characteristics or dosage form requirements can be used to select the right solubilization technology?

Dan Dobry: When choosing a formulation approach for low-solubility compounds, it's important to understand the following properties: 1) tendency of the molecule to crystallize, 2) lipophilicity, 3) dose, 4) solubility (aqueous and organic), and 5) presence of ionizable groups. Based on our experience of formulating over a thousand compounds, Bend Research has developed a number of flow charts and other guidances for choosing a formulation using a technology agnostic approach. Oral dosage form selection is generally dependent on the phase of development. Many of our clients prefer suspensions or capsules for Phase I because these forms make for facile dose escalation. Later stages of development can take the form of tablets, capsules, or modified-release dosage forms. The choice is dependent on many factors, including pharmacokinetic performance and target product profile or image.We work closely with our partners and clients, using science and engineering fundamentals to provide reliable, rapid, low-risk compound advancement.

Tom Dürig: Our major solubilization technologies are polymer based and involve the formation of amorphous drug-polymer dispersions. Critical drug characteristics include dose, glass transition and melting temperatures, ionic behavior (drug pKa), stability, and hydrophobicity as indicated by partition coefficient (log P). Dose-per-unit dosage

"Amorphous physical stability prediction has come a long way…"

Dan Dobry,
VP, Bend Research-
Dan.dobry@bendresearch.com

form is particularly critical as solid dispersions usually require a large portion of polymer (typically higher than 50%) for stabilization and solubilization. When the dose exceeds 400 mg, this can lead to obvious patient administration and compliance issues due to dosage form size. Additionally, the dose-to-solubility ratio is a key indicator of the solubility challenge that a given compound presents. We typically adjust polymer loading based on crystallization propensity, which can be approximated by the ratio of the glass transition and melting temperatures. If thermal processing, such as hot-melt extrusion (HME), is desired, then drug melting points below 180˚C and good thermal stability are valuable.

For spray-drying, we focus on drug and polymer combinations with good solubility in organic solvents, such as acetone and methanol. Drug ionization behavior (pKa) is important when ionic polymers are used as solid-dispersion carriers because the ionic interaction between API and polymer could be the key factor that impacts dissolution and stability of the solid dispersion. For instance, we have achieved particularly good solubility results for weak base compounds, like itraconazole, using AquaSolve™ L HPMCAS that has more succinoyl groups. In contrast, for weak acids (neutral or basic pKa), such as felodipine and ezetimibe, AquaSolve H HPMCAS with more acetyl groups is particularly effective in improving solubility.

Joan Feixas: Pharmaceutical cocrystals (multicomponent crystal API - coformer) are currently recognized as a preferred alternative to optimize API physico-chemical properties, such as solubility and dissolution rate without chemical modification of the drug substance. This technology is especially indicated for non-ionizable or poorly ionizable APIs. A co-crystal can also be used instead of a salt when it is not possible to obtain a solid or crystalline form of the salt, when the salt formation results in chemical degradation or when there is a risk of crystalline transformation to a less-soluble form during formulation or storage.

Filipe Gaspar: Physical and chemical properties of the drug substance, such as melting point; logP; chemical, thermal, and physical stabilities; release mode; and dose level, all play an important role when selecting the stabilization platform and the formulation approach. Soft gels may apply for low-dosage and very hydrophobic compounds, nanoparticles may apply when bioavailability is dictated by dissolution rate, and solid dispersions seem to have the broadest application of all. Once a platform is selected, the question is to decide on the manufacturing technology. For solid dispersions, spray-drying works for nearly all compounds and HME, when applicable, is likely to be a more cost effective technology.

"…API in suspension in a lipid-based vehicle can be used to deliver higher doses."

Keith Hutchison,
Senior VP of R&D Dosage Form Solutions,
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"There is a common misconception or exaggeration regarding the inherent instability of amorphous formulation systems."
Dave Miller, PhD,
VP of R&D, Dispersol Tech -
Dave.miller@dispersoltech.com

Robert Hoerr: The ability to get a BCS class II or IV compound into a solubilizable form is what guides most decisions to use solubilization technologies. Nanocopoeia is a therapeutic particle engineering company providing nano-enabled particle design, services, and equipment to the pharmaceutical industry. Specific to ElectroNanospray™ (ENS) nanoformulation, the most important API considerations are solubility in organic solvents, the need to reduce or eliminate problematic excipients, and the desire to protect, stabilize, and/or control the release of the API at the point of delivery.

Keith Hutchison: The combination of a number of key physical, chemical, and biopharmaceutical API properties tends to drive formula development and optimization in lipid-based liquid/semi-solid compositions for poorly soluble compounds. Key chemical and physical API properties include molecular weight, crystalline melting temperature, aqueous solubility, pKa, apparent partition coefficient, and polarity. Beyond these fundamental characteristics, compound solubility in lipid excipients, surfactants, and co-solvents is important to achieve adequate drug loading per unit dose. In some cases, API in suspension in a lipid-based vehicle can be used to deliver higher doses.

Dave Miller: The most successful applications of DisperSol's KinetiSol® technology are those involving insoluble compounds that require supersaturating delivery systems to enhance oral absorption and are also difficult to process by spray-drying and melt extrusion. Specifically, our technology is amenable to the production of amorphous solid dispersion systems with insoluble compounds having one or more of the following issues: high melting point, thermal sensitivity, poor organic solvent solubility, and/or requiring concentration-enhancing carrier polymer(s) that are thermally labile or highly viscous. KinetiSol is a novel fusion-based technology with very brief processing times at elevated temperatures (< 5 sec); therefore, the process is able to generate amorphous solid dispersions with thermally labile compounds and polymers that would degrade by melt extrusion. The process also offers mixing intensity an order of magnitude greater than melt extrusion, which enables compound solubilization in a carrier polymer well below its melting point and enables melt processing of highly viscous polymers without the need for plasticizers. The technology offers all the advantages of non-solvent processing and is particularly applicable when poor organic solvent solubility limits the use of spray- drying. When compounds exhibit high melting points or thermal sensitivity in addition to poor organic solvent solubility, KinetiSol if often the only viable amorphous solid dispersion processing technology.

Peter Nelson: The decision to evaluate particle size reduction via micronization (jet-milling) and/or mechanical milling can typically be made based upon three major API characteristics/requirements: particle size of the synthesized API, crystallinity, and thermal stability. If the particle size of the synthesized API is among the solubility rate-limiting factors, micronization or mechanical milling can be employed to effectively reduce the particle size to the desired range. This assumes, of course, that the required particle size is attainable via dry milling. If the API is required to be in a crystalline form to be effectively formulated, micronization is again a viable option. Our studies have shown that the micronization process retains drug substance crystallinity and that amorphous content (when present) is typically negligible. Finally, drug substances exhibiting poor thermal stability may benefit from the micronization process. Jet milling is a thermally neutral process.

Deepak Tiwari: At Particle Sciences, we have a number of solubilization approaches ranging from in silico design to solid solutions to lipid-based systems, such as LyoCells®. So, it is more of a question to which technology do the API's characteristics drive one toward. For instance, a heat-stable highly potent compound with a positive log P naturally drives toward HME, while a heat-labile molecule with a positive log P can be converted to amorphous form utilizing spray drying. Another approach for a relatively labile molecule with good lipid solubility would warrant looking at LyoCells, and of course, a classic BCS II

"…some drugs that were considered to be salts when approved, turned out to be co-crystals."
Joan Feixas, PhD,
CEO, Enantia -
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molecule should always be evaluated for its amenability to crystalline nanoparticles.

INTRACTABLE APIs

Q: Are there physical & chemical properties that typify an "intractable" compound?

Dan Dobry: Our experience at Bend Research is that many of the factors that typify an intractable compound can be dealt with using a science-based approach. That being said, an intractable compound can be typified in several ways through the lens of performance, manufacturability, and stability. For example, compounds with extremely low aqueous solubility (< 1 µg/mL) or low permeability (typified by ionic state, molecular weight, and polar surface area), may be considered intractable from a performance perspective. However, the appropriate enabling technology can often achieve the desired oral absorption. Intractable compounds from a manufacturability perspective tend to be typified by low solubility in processing solvents, which is generally translated to having extremely high melting points (> 230°C, generally considered to be brick dust) or compounds that have very low glass transition temperatures (< 50°C). Formulation and process approaches can be utilized to enable these compounds in many cases. From a physical and chemical stability perspective, compounds that have extremely low glass transition temperatures (< 50°C), high melting point to glass transition temperature ratios (> 1.35 K/K), and chemical functionality known to be labile to hydrolysis or

"There is the misperception that spray-drying is not adequate for processing thermal labile drugs…"
Filipe Gaspar, PhD,
Director of Drug Product Technologies,
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oxidation tend to be considered intractable. In these cases, functional excipients will be required to stabilize either the amorphous state or to block the chemical reactivity and lead to a stable product. It is worth noting that despite a compound having intractable properties, dose can often be the leading factor in exacerbating or minimizing the extent of the challenge to deliver the molecule.

Tom Dürig: The most intractable properties would include high crystalline-lattice energy and high lipophilicity. APIs that have extremely low solubility in all commonly used spray-drying solvents and/or that demonstrate thermal instability could present significant challenges during process development.

Joan Feixas: Regarding the question of intractable compounds, almost all the APIs are possible candidates to be used to form cocrystals. However, the probability of success decreases with fewer chemical functions bearing hydrogen-bonding acceptors or donors, fewer aromatic rings to form pi-stacking, or the presence of a high structure flexibility.

Filipe Gaspar: The most challenging compounds include compounds from BCS class 4 and those that combine very high melting point with low-solvent solubility.

Robert Hoerr: Intractable compounds are typically very poorly soluble and also poorly permeable (i.e. Class IV compounds.) Strategies for oral administration often require unique (and expensive) technologies and often use alternative delivery methods, such as intravenous administration. In the case where delivering a Class IV compound orally is the goal, the improved solubility at the absorptive surface that an amorphous solid provides may be insufficient to generate the required permeability. Nanoformulation, such as nanocrystal suspensions, has provided some improvement in bioavailability. The ENS approach could be extended to BCS class IV drugs by spray excipient combinations that encapsulate or otherwise modify surface chemistry to facilitate permeation.

Keith Hutchison: Occasionally, a high dose, poorly lipid soluble, low permeability compound comes along that would be a typical intractable compound. We also consider the biopharmaceutical aspects of the API, such as rate of aborportion and clearance, P-gp efflux potential, and lymphatic drug transport - these API characteristics further guide our formulation design.

Dave Miller: An intractable compound for the KinetiSol process would be one that is extremely thermally unstable at elevated temperatures in its amorphous

"…drug substances exhibiting poor thermal stability may benefit from the micronization process."
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Director of Analytical Services,
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"The flexibility of electrospray technology can provide highly improved, homogeneous mixing of drug and excipient in varying ratios."

Robert Hoerr MD, PhD, Co-Founder, Chief Scientific Officer, Nanocopoeia, Inc. - Bob.hoerr@nanocopoeia.com

form, ie, rapidly degrades in seconds at elevated temperatures. Also, compounds that are chemically unstable in the amorphous form at common storage conditions can be very difficult to manage with KinetiSol, as with all amorphous dispersion technologies.

Peter Nelson: There are a few physical and chemical properties that would make an API "intractable" for micronization. For example, an API that will not readily fracture would not be a good candidate for micronization. We have seen very few APIs, however, that are not able to be reduced in size. The question becomes whether or not the size attainable via micronization produces the desired results. Any API that has been synthesized to a size consistent with "micronized" powder (ie, less than 10 microns) could present a challenge for further size reduction. Compounds with low melting points can be considered "intractable" where mechanical milling (eg, pin-milling or hammer-milling) is required. Mechanical milling may produce sufficient heat to melt the API. Hydrates may also be challenging to work with in cases where increased surface area produces API that is overly susceptible to moisture loss under low relative humidity. This becomes less of a concern when the micronized product is exposed to adequate moisture and permitted to re-hydrate. In most cases, there are ways to address the physical and/or chemical challenges associated with most APIs. Ultimately, the decision to micronize is based on whether or not the increase in surface area produces the desired level of bioavailability.

URBAN MYTHS

Q: Are there urban myths about when to use or to avoid a specific solubilization technology that diminish opportunities for solubilization?

Dan Dobry: In the past, it was common to hear concerns about formulations relying on amorphous APIs. In particular, there was a great concern about physical stability and the need for what were perceived as new technologies, such as extrusion, spray-layered coating, or spray-drying. With the commercialization of compounds, such as Kaletra, Incivek, Zelboraf, Kalydeco, and other amorphous APIs, it has become accepted to use non-crystalline approaches for delivering low-solubility compounds. Amorphous physical stability prediction has come a long way, including use of predictive tools as an approach to de-risking long-term stability studies. It's possible to accurately predict worst-case stability using rapid measurement techniques in combination with theory on the fragility of glasses. Bend Research scientists are happy to describe the methodology, case studies, and theory for kinetically stable glasses with those interested. Understanding the role that processing plays in creating these stable forms is also much better understood now - especially using spray-drying.

Tom Dürig: Frequently, when a compound has solubility-limited absorption, nano-crystalline material is of limited use because it does not affect API solubility. For a compound with strong crystal-lattice energy and medium-to-low log P, lipid formulations are often not a very effective solubilization approach. For very high log P and/or high crystal-lattice energy APIs, solid dispersions tend to suffer from low drug loads.

Joan Feixas: Until recently, the pharmaceutical cocrystal approach has not been a preferred option in the pharmaceutical industry because there are no marketed drugs formally approved as cocrystals. However, the reality is that some drugs that were considered to be salts when approved, turned out to be cocrystals. The interest in cocrystals is clearly growing as evidenced by the increase each year of the cocrystal patent number. Today, there are a number of pharmaceutical cocrystals progressing through clinical trials, and it is only a matter of time before some of these will be commercial. Then, we will be able to speak of "official" pharmaceutical cocrystals.

Filipe Gaspar: There is the misperception that spray-drying is not adequate for processing thermal labile drugs or that the low yields at bench scale are representative of the technology. In fact,

"Nanotechnologies are diverse with different manufacturing processes and mechanisms of stabilization..."

Deepak Tiwari, PhD, Director, Formulation & Process Development, Particle Sciences, Inc. - dtiwari@particlesciences.com

the technology is very gentle from a thermal viewpoint, and any reasonably developed process, at the right scale, delivers yields of at least 90%, more often 95% to 98%. For HME, it is commonly supposed that the technology cannot be used in high melting point drugs, but in some cases, dissolution in the polymer occurs at lower temperatures.

Robert Hoerr: Historically, amorphous forms of API have been deemed thermally unstable and therefore unsuitable for meeting environmental and shelf-life requirements. The flexibility of electrospray technology can provide highly improved, homogeneous mixing of drug and excipient in varying ratios. Multiple streams allow for a wide range of ratios that can include nano-sized or molecular subcomponent in solid dispersions or solid solutions. Targeted ratios can show improved solubility, suspendability, and dispersability while not compromising or even improving thermal stability.

Keith Hutchison: A common myth is that each solubilization technology is mutually exclusive whereas in fact there is sometimes considerable overlap between different technologies. For example, an API produced in a nanoparticle form and also solubilized in a lipid-based formulation may show similar bioavailability in fasted subjects; however, if the API has a positive food effect, the lipid formula is most likely to overcome this particular issue in a fed study. In addition, a high log P is not always necessary to produce a lipid formulation (though it might help) because a less lipophilic API can still be solubilized in a lipid-based formulation, particularly if the compound possesses a low melting temperature and/or is low dose.

Dave Miller: There is a common misconception or exaggeration regarding the inherent instability of amorphous formulation systems. While it is true that for most compounds, the neat amorphous API is physically unstable/metastable and will eventually convert to the lower energy crystalline state, this is not true for properly designed amorphous solid dispersion systems. By utilizing appropriate in silico and empirical tools, one can design an amorphous solid dispersion formulation that is either thermodynamically stable, or is kinetically stable for a period of years at typical storage conditions. The anxiety regarding the myth of inherently unstable amorphous systems has very likely limited the application of amorphous dispersion technologies for developing compounds whose therapeutic potential may not have been realized as a result.

Peter Nelson: A common urban myth related to micronization suggests that the micronization process produces excessive amorphous content and may lead to crystalline phase transitions. While some level of amorphous content may be generated under aggressive milling conditions, the % amorphous content is typically very low. Our own testing of hundreds of micronized APIs via XRPD, DSC, and other techniques indicates that true crystalline phase transitions seldom occur as a result of the micronization process.

Deepak Tiwari: We occasionally see nanoparticles as a class being ruled out because one or another approach failed. Nanotechnologies are diverse with different manufacturing processes and mechanisms of stabilization, so failure in one has little bearing on the chances of another.

THE NEXT ISSUE

In Part 2, we'll hear more from solubilization technologies experts, including innovative ways to leverage and combine technologies to expand opportunities for overcoming poor solubility. To ensure *The Second Quadrant* serves as a forum for interactivity and collaboration, I invite you to send your reactions, thoughts, and suggestions so we can continue our dialogue. I look forward to hearing from you. ◆

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Trends in Skin Medication Dispensing

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

INTRODUCTION

Skin diseases are among the most common diseases worldwide. Approximately one third of the population is affected with a pathological skin problem during their lifetime. In 2010, the total dermatology drug market has been valued at $26.8 billion and is estimated to grow at a CAGR of 3.7% until 2015. This growth will slow down during subsequent years reaching an estimate volume of $37.8 billion in 2026.[1]

Up to 25% of total healthcare spending is for dermatology conditions. So dermatology is certainly not a niche market. Within the five largest European Union countries (EU5) almost 70% of skin medications are prescription-only drugs. This split is considered to reverse throughout the next years in favor to over-the-counter (OTC) products due to the following observations:

- The number of new drug molecule entries into the dermatology market is not projected to increase.[2]
- Price regulation and pressure will lead to increasing numbers of switches from prescription to OTC availability of medication. The OTC market still allows for more freedom in price positioning.
- As most skin diseases are not life-threatening and often considered a "nuisance" rather than a disease, many patients do not seek physicians' help.

In addition to the well-documented use of medicated drugs, there is a large market of non-medicated skin care products: emollients, skin cleansers, or hydration and protection products, among others. The following focuses on trends in topical skin medication, the impact on primary packaging, and possible dispensing solutions.

CURRENT PACKAGING FOR SKIN MEDICATION

In 2011, almost 500 million units of topical skin medication have been sold within the EU5 countries. More

FIGURE 1

Jar systems with means of a piston system pushed from the bottom either manually (left, Unguator®) or using a turn system (right, Aponorm®).

than 90% of these products have been of semi-solid formulations, such as lotions, creams, ointments, gels, pastes, or foams. The remaining share has been evenly split into liquids and powders.[3]

Tubes are well established and often the first choice for most semi-solid drugs. The simplest and cheapest version is the single layer plastic tube. But barrier function (light, evaporation) is somehow limited. Increased barrier function requirements can be satisfied by use of aluminum or multilayer tubes. The latter combine the barrier function of an aluminum layer with the look-and-feel of a tube. Tubes can be combined with a wide range of closures with different design and functionality. When a tube is opened, its content is exposed to environmental influences; drying and discoloration can occur. Also, dosing and emptying is greatly dependent upon tube type and user experience. Notably, aluminum tubes are prone to breakage and leakage if not properly handled.

The use of jars in topical dermatology is easily explained by the need for easy access to the final product. Pharmacy-made formulations and reconstituted medications often require a large opening. In turn, this also means a large surface in contact with oxygen and allowing for evaporation. Some systems try to limit environmental influences. Additionally, attempts have been made to have better control while dispensing product (Figure 1).

FIGURE 2

Dispensing systems preventing air intake. From left to right: flexible lips for dispenser heads or tube closures (Aptar), self-closing mechanisms by use of elastomer (Megaplast) or mechanical elements (Aptar).

Liquids and low-viscous products are often filled into bottles. While colored glass bottles offer the best barrier functions (evaporation, light protection), plastic bottles are often preferred because of the lower risk of breaking. In order to increase barrier functions, special plastic bottles incorporate a co-blow-molded multilayer bag inside. Basic screw and flip-top closures are very common in combination with bottles but bear the risk of drying and discoloration of product around the orifice. The high-end version of a bottle closure is the pump dispenser, which helps deliver a consistent dose of product with each actuation.

Other primary packaging types used in skin medication include pouches, sachets, or stick packs for single doses, airless dispensing systems, or aerosols, including bag-on-valve (BOV) systems for multiple uses. In addition to these standard dispensing systems, a range of specialized and often customized packaging solutions has been created.

TRENDS IN SKIN MEDICATION

Some trends in the topical dermatological market begin to change the way these drugs are presented to the end consumer. Trends that drive this change and, therefore, are important to the pharmaceutical industry include:

- changes in life-style and demographics
- increased awareness of drug safety
- pressure to deliver cost-efficient treatments
- drying pipelines of drug innovation
- pressure to differentiate existing products from competition

In addition to these general challenges, skin medication requires a special focus on protection of mostly semi-solid drug products, convenient dosing, access to difficult-to-reach body areas, and lesion-directed treatment.

FIGURE 3

Applicator systems to help with lesion-directed dispensing. Digital Airless with finger-like applicator head. SofTips tube closure with soft touch silicone lips (Aptar).

PROTECTION FROM ENVIRONMENTAL INFLUENCES

It is likely that innovative drug formulations will demand increased protection through primary packaging. Shelf storage for up to 3 years is followed by an in-life period of a few weeks. Following first dispensing, remaining product on the dispensing system tends to dry or potentially crystallize. This is particularly observed with viscous formulations in which drying product can lead to clogging and subsequent malfunction of the dispensing system.

Topical dermatology products often use fatty or oily auxiliary components to enhance the retention on and uptake of the drug substance through the skin. Such formulations are often sensitive to a variety of environmental influences. Exposure to sunlight or oxygen can lead to deterioration of drug substance activity as well as development of unfavorable color.

Intake of moisture from the environment into the formulation or evaporation of water or solvents from the package will potentially lead to deterioration of content. Consequently, diffusion has to be eliminated by use of appropriate packaging material providing sufficient barrier function.

During the in-use period, the orifice of any dispensing system is the most challenging region. Clogging due to drying product is actually the most often reported complaint. Standard pump systems represent a constant barrier to outside air in itself. However, at the outer part of the dispenser, they will not avoid oxygen exposure or clogging due to evaporation. Therefore, modern pump dispensing systems are designed in such a way that the orifice is closed between the actuations. This prevents entry of air into and drying of the medication within the system. Different technical options are available on the market. Flexible closing lips support clean dispensing and help protect against air intake during periods of storage. Self-closing mechanisms can be designed into pump actuators to better protect dispensing orifices (Figure 2).

If product is dispensed from a vented system, ambient air will replace the dosed volume in the container and consequently get in contact with the remaining product. This may be critical for oxygen-sensitive drug products. In such situations, so-called unvented or airless packaging systems should be used. In these airless systems, moving parts (tow piston) or collapsing bags compensate for the volume of the dispensed product. In such systems, the wall of the container must be able to barrier against oxygen diffusion. Alternative systems use a plastic or aluminum bottle to provide the desired outer shape and use aluminum or multilayer inner bags to contain the product.

PROTECTION FROM MICROBIAL CONTAMINATION

To keep microorganism levels in the product low during the in-use period, most often, preservatives are used. Especially in patients with diseased skin, preservatives are a potential source of additional irritation. For example, parabens (ie, para-hydrobenzoic acid esters) have come under scrutiny after observation of contact sensitization exacerbating in patients with inflamed or broken skin. Even if paraben levels nowadays are below limits where they are generally recognized as safe, they have been eliminated from most skin medications. However, the use of other preservatives that serve as replacement bears the same concerns about irritation. Therefore, an increasing amount of

preservative-free formulations are entering the skin medication market.

Primary packaging and dispensing systems that are able to handle non-preserved drug products need to prevent bacterial ingress into the drug product. These dispensing systems build a physical barrier to microbes at the interface to the outside. Sealing needs to be sufficiently strong to break product micro-films. Modern systems make use of elastomer elements or spring-loaded tips sealing the dispensing orifice. They can effectively protect non-preserved formulations or allow for lower concentrations thereof.

Another source of microbes is venting air. Whereas non-vented packaging prevents contamination by avoiding incoming air, sophisticated systems allow incoming air to pass through layers of filtering micro-membranes.

CONSUMER CONVENIENCE

A substantial number of dermatological diseases require daily use of skin medication. Therefore, dispensing systems should be convenient, supporting patients' adherence to long-time treatment. Smooth actuation and good control of product flow can be obtained from non-metered systems (eg, BOV, tube). But obtaining a consistent amount of medication as appropriate for the diseased skin area is difficult and very much user dependent. Precise dosing recommendations are not easily provided. Commonly, these are either describing the thickness of product layer onto the affected area (eg, "Cover … with a thin film of…"), make use of comparisons to phalanges, or provide card box rulers together with the medication package.

Metered dispensing systems for lotions or creams are available using precision pumps. Delivering a consistent dose per stroke from a metered pump system enables the patient to have the same amount of product used each day. Thus the prescribed dose is ensured, and safety concerns regarding overdosing are minimized.

PRODUCT DISPENSING & APPLICATION

In dermatological disease, the skin is often inflamed or broken, and therefore sensitive to direct contact. Formulations that can be applied easily and homogenously are preferred. Target lesions might be anywhere on the body or even very small. Therefore, packaging that supports dispensing to difficult-to-reach body areas is appreciated.

Liquids can be applied by continuous valve or metered pump dispensers creating a soft spray without any need to touch skin areas that are sensitive or inflamed. Likewise, skin medication formulated as foam or mousse ensures smooth spread across the area to treat. Aerosol foams are commonly created by use of pressurized packages in combination with specialized foam actuators. More recently, innovative mixing and filling techniques in connection with BOV systems allow for the generation of mousse from a semi-solid preparation. BOV technology does not require the use of a propellant as part of the drug formulation. Instead, pressurized air in the outer container is used to deliver the bulk from a separated inner pouch. Pump foamers are non-pressurized systems that are mainly used in skin cleansing and care.

By using specialized applicators in combination with small-volume pumps, skin medication can be directly applied to a tiny target lesion. These applicators can be designed for dispensing medication on-the-spot, avoiding the need for additional use of finger tips (Figure 3). In situations where other persons give care to a relative or child, this might be appreciated.

FIGURE 4

Convenient dispensing systems for everyday use. Aptar Bag-On-Valve and small piston system for carry-on.

FIGURE 5

Aptar creative design for differentiated products. Innovative packaging for modern consumers: pen dispenser study, bottle design.

LIFE STYLE

Stigmatization of patients in need for medical treatment should be avoided. Especially for certain patient groups like teenagers with acne, peer group pressure can lead to treatment discontinuation and non-adherence. Ideally, treatment regimen and dispensing should match a patient's daily schedule, activity, and capability. In consequence, dispensing systems might be targeted to different user groups. Mobile and active life style or an increasingly aging population with, for example, limited dexterity, are two examples of related mega trends in the Western population.

Medication that is handy at the time the patient needs to use it is more likely to be taken. Therefore, dispensing systems need to be limited in size and robust enough to be carried around in a sports bag or purse. Small airless pump systems and BOVs offer a convenient size, protect the medication from influence of air, leakage, or damaging impact, and provide good control of dispensing (Figure 4). Dispensing systems that appear pleasant, trendy, or look like "just another cosmetic," are likely to enhance acceptance.

SAFETY

There is an ever-increasing amount of information delivered together with pharmaceutical products. Despite efforts to improve readability and comprehension of printed patient information, it is common belief that most patients do not properly read this.[4] Self-explanatory and convenient dispensing systems can support correct and safe use. Key instructions repeated on the dispensing system, symbols to guide the patient, and finger flanges providing tactile feedback during dispensing are only some examples that help intuitive use.

On the other hand, such intuitive guidance should be introduced cautiously. Symbols may be interpreted differently in different regions of the world. Understanding of design features might not be the same with every cultural background. Consequently, regional consumer input into innovation is key to develop successful dispensing systems that add value to the drug product.

To prevent contact with potentially harmful medication (eg, hormones, minoxidil) by unattended children, special primary packaging incorporating child-resistant features may become mandatory.[5] Push-and-turn solutions that are used for tablet containers are already implemented as a bottle or tube closure. Over-cap solutions that are known from household chemicals can be implemented in packaging for pharmaceuticals. Locking mechanisms integrated into the dispenser head offer the benefit of not being accidentally separated from the medication package during use.

Introducing safety features into pharmaceutical packaging always has to be balanced with accessibility.

The megatrend of demographic shift will lead to increasing numbers of elderly consumers. Patients with limited dexterity or poor eyesight might have problems to access the drug product at all. Innovative packaging solutions can help improve accessibility to medication and compliance to treatment schedules (eg, triangle-shaped closures or bottle shapes).[6]

PRODUCT DIFFERENTIATION

The increasing number of drugs put on the market has led to increased competition. Therefore, brand recognition plays a major role in a situation where patients are well educated, have access to multiple sources of information, and are faced with increasing out-of-pocket expenses when buying medicine.

Next to efficacy and safety of a drug, attractiveness of the package, convenience, and differentiation together help generate consumer loyalty. Dispensing systems that offer additional characteristics will provide potential to stick out from the crowd. Innovative design in bottle or container shape will offer product recognition (Figure 5). The use of custom-made applicator systems will not only enhance convenience but also help create a dispensing experience that will last in the mind of the patient.

SUMMARY

Traditional packaging of topical medication appears to be almost boring, but new delivery devices are on the horizon. Primary packaging systems for topical dermatological products face different challenges but at the same time, are offering great opportunities. Depending on the needs, the content will be protected from environmental influences, such as oxygen, light, or drying and clogging. New systems are able to block microbial contamination and will help reduce or even avoid the need for potentially harmful preservatives. Ideally, innovative dispensing systems support long-term treatment schedules through attractiveness, convenience, intuitive design, and match with the daily activity of the patient.

Early life-cycle management of a drug changing from a more common to innovative packaging systems bears the opportunity to create a new brand image, to retain existing or attract new consumers, and to differentiate from competition. ◆

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BIOGRAPHIES

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

Dr. Degenhard Marx, following the study of Veterinary Medicine and the successful completion of his thesis at the University of Leipzig, joined the Arzneimittelwerke Dresden/Asta Medica co-operate research in 1992. In 2001, he took over a Senior Research position at Altana Pharma/Nycomed in Constance, Germany. During this time in the pharmaceutical industry, he collected ample experiences in the drug development of anti-inflammatory and cardiovascular drugs. In 2008, he became Business Development Manager at Ing. E. Pfeiffer, Pharma Division, which became Aptar Pharma in 2010. He is now Director of Scientific Affairs within the Aptar Pharma Consumer Health Care division.

DRUG DEVELOPMENT Executive

VETTER
Answers that work

VETTER: SUCCESSFULLY BRIDGING THE INNOVATION GAP IN DRUG DEVELOPMENT & MANUFACTURING

Claudia Roth, PhD
President,
Vetter Development Service Chicago

"We are noticing that CDMOs are acting more and more as the interface between small biotech firms and large drug manufacturers. This is due to a variety of reasons, including the fact that an internationally leading CDMO by definition has already reacted to the changes in the world of R&D."

Pharmaceutical and biotechnology companies are under increasing pressure due to sustained globalization in the industry with the associated risks and the loss of patent protection for many blockbuster drugs, resulting in tremendous competition from generic drugs. Generics are projected to grow from $242 billion in 2011 to $430 billion in 2016, according to an outlook report from IMS Institute for Healthcare Informatics. To lower the overall company risk, large pharma/biotech companies have cut back on their own research and development spending and prefer buying advanced promising candidate technology and compounds from small biotech companies as part of their innovation strategy. This enables them to move new injectable drug developments forward while at the same time, limits their own financial risk. For these companies, however, this strategy demands compliance on the part of the biotech partner with high quality, safety and efficacy standards as a precondition. Only the reliable implementation of these preconditions will enable performing clinical trials and subsequently commercialization efficiently. Due to financial constraints, small biotech firms trying to focus on proving the effectiveness of their drug substance encounter challenges and regulatory obstacles that can impede their efforts. By not maximizing the value of their compound in the early stages of drug development, they miss the major opportunity to attract investors, provide out-licensing opportunities, or in some cases, even outright acquisition by one of the large pharma/biotech companies as mentioned above. Drug Development & Delivery recently interviewed Dr. Claudia Roth, President of Vetter Development Service in Chicago, to discuss how an experienced CDMO can help bridge the gap of different parties' focal points and be of vital support in the process of injectable drug development.

Q: For our readers who are not yet familiar with your company, can you briefly discuss Vetter and what service portfolio it offers?

A: Vetter is an independent contract development and manufacturing organization (CDMO) headquartered in Ravensburg, Germany, and specializes in the aseptic filling of syringes, cartridges, and vials. We have extensive experience with biologics and other complex compounds, including monoclonal antibodies, peptides, interferons, and vaccines. As a full-service provider, we support our customers' products throughout their lifecycles, from preclinical development through global market supply. We operate state-of-the-art facilities in the US and in Europe that provide support for early stage drug products, with seamless transfer at Phase III to Vetter Commercial Manufacturing for large-scale production. We are the originator of dual-chamber technology, which enables easier, safer lyophilized drug administration; and are a leader in the use of RABS technology in cleanrooms, which mitigates risk of product contamination throughout the manufacturing process.

As a family owned, independent company, we do not manufacture our own drugs, but focus solely on our customers' product success.

Q: Can you identify what you see as some of the key trends in the manufacturing industry today, particularly as it applies to the small biotech firms versus large pharma/biotech companies?

A: The R&D model that we saw in the industry just a few years ago continues to rapidly evolve. These changes have been largely due to the ever-increasing costs associated with drug discovery and development, including the time necessary to do this increasing complicated job from the very start and the tremendously increasing pressure to compete and innovate. In addition, the industry faces stricter regulatory guidelines than ever before. To overcome these hurdles, we have seen a continuing trend toward collaboration between big pharma/biotech companies and small biotechs.

In many of these cases, we have observed outright acquisitions or mergers between companies. For the large company, the acquisition of a smaller one with promising injectable drug candidates or advanced technology is an attractive option. It affords them the opportunity to move new drug developments forward while limiting their financial exposure or risk. For the small biotech company with limited resources, access to greater human and financial resources allows them to better focus their attention on pursuing other promising injectable drug candidates. Thus, it can be a win-win for all, each focusing on its core competencies. However, the key to a successful partnership or the key to a successful out-licensing deal will be generating a harmonization of requirements that meet the needs of both parties.

Q: Can you provide insight on how the needs of large pharma/biotech companies differ from the ones of small biotech companies?

A: At first glance, it would seem that both have the same target; develop and bring to market injectable drugs and technologies to help patients, while achieving regulatory compliance. But that is pretty much where the similarities end.

Large companies need to minimize their risk and ensure they reward investments from a commercial perspective. That equates to high quality, safety and efficacy standards being a precondition of any partnership or acquisition strategy. Offering innovative solutions that will meet a variety of market needs while achieving packaging and process flexibility is the pathway to success. Also, later product lifecycle management activities for long-term market success are key targets.

It is these attributes that small biotech companies often lack in their early approach, potentially creating the formula for a successful partnership or acquisition. With their start-up culture and primarily scientific know-how, they focus on the rapid development of drugs and technology. Having said this, they often lack or have little experience in packaging issues, process development, manufacturing, regulatory, or commercializing the drug. Also the end-user perspective is not yet part of their overall project scope.

Furthermore, they are extremely sensitive to any risk in early clinical phases because they are typically less resourced from a personal and a monetary aspect. If the compound performs poorly or fails in drug development, the very survival of the company itself can be imperiled. Thus, little thought in this stage is been given to the later development or commercialization efforts that must be applied to the compound.

Q: You stated earlier that in order to ensure success for both companies, harmonizing their individual requirements is critical. Can you offer some thoughts on which approach small biotech companies often follow in their drug development?

A: Small biotech companies often lack the knowledge and resources necessary for developing their drug product beyond the current early development phase. This lack leads to a gap that makes it difficult to leverage efficient and lean processes while achieving high quality, safety and efficacy. Small biotechs may believe the simplest solution is a cooperation with a variety of small, local laboratories and filling services or generally speaking, single-service providers.

This can present a problem, however, because the small, local service providers seldom possess essential experience and hands-on practice in dealing with complex drug substances and their special requirements. They may also lack the long-term regulator relationship required for the smoothest possible regulatory approval. In the case of injectable drug filling, the small single-service providers are often limited to manual filling operations, targeted to rapid filling realization. This can harbor risks in terms of both drug quality and safety.

As I noted earlier, large companies must ensure that quality and safety standards are met in performing clinical trials to help bring about the eventual efficient commercialization of the drug. Only operating with such standards enables them to successfully perform their strategy: move new injectable drug developments forward while limiting financial risks.

Q: How can a CDMO help?

A: We are noticing that CDMOs are acting more and more as the interface between small biotech firms and large drug manufacturers. This is due to a variety of reasons, including the fact that an internationally leading CDMO by definition has already reacted to the changes in the world of R&D.

Such a full-service partner has long-term experience with a variety of compounds, including very complex ones, and has knowledge of the most recent regulatory guidelines. Professional CDMOs have set up specialized development services portfolios in the markets where innovation is happening, and often can provide the appropriate capacities and services in the US and Europe.

For the small biotech company, partnering with a CDMO affords support in realizing faster and more efficient drug development, and adds critical added value from the earliest stages due to the combination of efficiency, long-term thinking, and high quality and safety. The CDMOs' packaging, process, and manufacturing know-how as well as the broad compound experience is included right from the start. Lean and streamlined processes with professional project management and success-oriented guidance supports the progress as well as time- and cost-savings. Complete customer-control is included in every development project step due to ongoing direct communication flows between all involved project members.

By turning to an experienced CDMO, sponsor companies get support in avoiding obstacles and, at the same time, facilitate a lean and efficient clinical drug development. This helps contribute to the likelihood of out-licensing and in the end, monetary value of their drug products. Larger companies can benefit from this approach when acquiring a drug substance or the small biotech company as a whole.

So for both small and large companies then, a CDMO can act as the interface between each other, supporting to align the requirements of both companies, and thus the CDMO being an important key to bridge the gap.

Q: Are there more advantages for cooperating with a leading CDMO for small biotech or large pharma/biotech companies?

A: There are certainly distinct advantages for both the small and large companies when a CDMO is involved. Let us have a

closer look at some of the services a CDMO can provide, for example, the aseptic filling procedure. CDMO development services commonly have high-performance production capacities available for clinical filling. Their infrastructure often includes anything from semi-automatic equipment to fully automated filling lines for various drug delivery systems as vials, syringes, or cartridges. This service portfolio offers the small biotech company an opportunity to leverage efficient and lean processes while achieving high quality and safe results. It's also a way to improve their processes and reduce their time-to-clinic.

This, in turn, generates interesting criteria for large drug companies because they can then trust the reliability and high quality of successful drug developments. Having a CDMO as a partner will help not only to cover the actual development phase, but the support of the entire later process as well from approval and subsequent commercial manufacturing, which is already handled by the large company. By supporting the development of injectable drug substances from the start, the potential of expensive and time-consuming knowledge losses from changing single-service partners later is not an issue. The knowledge gained from the early development is kept safe and can be used later on for following processes.

As for the large drug company, having a CDMO that has the data and experience from handling the drug substance previously offers enhanced value. For example, following the acquisition of the biotech firm, the large drug manufacturing company can optimize processes themselves and thereby accelerate time-to-market.

Q: From your own perspective, how does Vetter differ from other leading CDMOs?

A: As one of the global leaders in aseptic contract development and manufacturing, Vetter offers a foundation of experience spanning more than 25 years, and dozens of successful pharmaceutical and biotech customer compounds. For Vetter, quality is one of the single most important aspects of our work because patients take into their bodies what we manufacture for our customers. We have passed more than 25 FDA inspections successfully. Our strategic approach can be defined in a single word: alignment. All decisions, both within the company and with our customers, small and large alike, are aligned to clear, specific goals.

It is expected that a CDMO partner for injectables offers among other criteria, quality, reliability, flexibility, and punctuality. These are the key factors necessary to achieve a successful partnership. Vetter invests in high-quality materials and aims to achieve the highest possible safety and cGMP standards. Based on our long-term and varied experience, we implement a highly structured project management approach. Combined with ongoing direct communication between all involved parties, this approach serves to reinforce mutual trust. A CDMO has to know and understand the needs of its customers and meet them accordingly. This is why we maintain a close and personal contact with our customers through our key account management organization. For Vetter, it is important to know what their needs are today, but crucial for us to also understand what support they will need in the future with their continuing development. We want to be in the position work with them in partnership to create new solutions. ◆

SPECIAL FEATURE

Hand Held Devices: New Technologies Right the Wrongs of Earlier Devices

By: Cindy H. Dubin, Contributor

One of the most significant trends today in the drug delivery industry is the ascendency of the injectable market. According to information reported by Datamonitor in 2012, injectables as a whole (including those delivered by hand held devices) are becoming the single largest driver of the pharma/biotech market. At an estimated growth of +3.6% for 2011 to 2016, injectables outstrip every other drug delivery category.

Thus, IMS Health has stated that by 2016, sales of injectable drugs will increase from the current $170 billion to more than $200 billion. While the growth rate for the established markets, such as North America, Europe, Japan, and Australia, is between just 1and 3%, growth in Asia and Latin America is much stronger at 12-13%. A sustained high level of growth can particularly be observed in China, India, Russia, Brazil, South Korea, Mexico, and Turkey.

The reasons behind the growing demand within the pharmaceutical market, which will continue to rise in the future, are an aging population and the sharp rise in prosperity in newly industrialized countries with the associated improvements in healthcare provision, explains Ian Thompson, Vice President, Business Development at Ypsomed.

The market for hand held self-injection systems is in transition and is expected to evolve over the next decade, primarily driven by three major factors, according to John Turanin, Vice President and General Manager, Zogenix Technologies. These are the increase in autoimmune disorders and the subsequent innovations in biologic drug therapies requiring injectable drug delivery; the increasing competitive mix within the biopharmaceutical industry, with the emergence of therapies, expanding pipelines, less differentiation, and the competitive threat of biosimilars; and FDA raising the bar for approvability of drug/device combination products by seeking evidence-based human factors design demonstrating usability in the intended population.

"All three of these factors are converging to increase the need for drug delivery alternatives that offer real and sustainable competitive differentiation and are preferred by patients actively involved in their healthcare choices," says Mr. Turanin.

The market is also being influenced by the growth of the homecare sector. The main markets include treatments for chronic conditions such as diabetes and hormone deficiencies where repeat injections are necessary and are administered by the patient or a caregiver.

"There is an increase need for safe and reliable drug delivery devices to be used in the home setting. More and more, patients want to self-administer, rather than have to travel

Studies demonstrate positive results for DosePro delivery of biomolecules and their typical viscous formulations (Zogenix).

Duoject's hand held delivery systems include the PenPrep Evo reconstitution system (left), E-Z-Link vial socket container (middle), and the VaccJect cartridge-based injection solution (right).

to a physician's office for regular injections, and payors are encouraging that more cost-effective option. The aging of the Baby Boomers coupled with patients who have serious, chronic diseases, such as multiple sclerosis or rheumatoid arthritis, seek user-friendly devices that fit into their lifestyles," says Peter Soelkner, Managing Director, Vetter Pharma International.

Another key trend is an increased need for delivery systems capable of containing and delivering injectable doses of greater than 1mL, either in a single-dose rapid shot, or slowly over a longer period of time. This trend is driven by the challenges of next-generation biologics, including increased concentrations and higher viscosities. For doses below 1mL, device manufacturers have reduced device complexity while improving the patient experience, especially when dexterity or cognition can be a factor.

"More than 1.3 billion 3mL insulin cartridges are manufactured each year, which is leading to a high level of demand for pen systems," says Mr. Thompson. The market for pre-filled syringes (1mL) for drugs manufactured using biotechnology is growing, with a current annual market volume of around 300 million units. Only around 8% of these are offered in conjunction with an autoinjector, he adds.

Despite the many drivers positively impacting the hand held delivery sector, there remains the challenge of overcoming the legacy of subpar performance of early designs of needle-free jet injection technologies left in the tracks of early-stage medical device companies, says Mr. Turanin. "These attempts created perceptions that needle-free technologies don't deliver accurately to the subcutaneous tissue, cause greater local site reactions than needle/syringe, will damage biomolecules, and are unreliable. Now, pharmaceutical scientists have objective data showing that these issues are a thing of the past. The industry has access to a needle-free technology that outperforms past attempts at needle-free delivery and has real technical and commercial advantages over current autoinjectors."

DUOJECT—FOCUSED ON RECONSTITUTION OF LYOPHILIZED DRUGS

Having been one of the leaders in the drug reconstitution and delivery market for nearly 30 years, Duoject's Simon Williams, Business Development, says the company is excited to witness the growth and interest that devices that enhance the safety and simplicity of drug reconstitution delivery are now receiving from the pharmaceutical markets. Mr. Williams states: "This trend is driven by the growing delivery of biotech drugs in the home market by inexperienced patients and care givers, but we also see a healthy growth in drugs intended for delivery in the traditional professional patient care environments. These professional use markets are focused on safety and time savings."

To meet the needs of both the home and professional patient care markets, Duoject offers several hand held delivery systems. Its lead hand held system, E-Z-Link, provides for the safe reconstitution of any dry form drug in a vial and diluent in any standard Luer Lock syringe. E-Z-Link is a vial socket

connector with a patented protective disc to reconstitute a solid form drug using any ISO standard prefilled diluent syringe and a traditional pharmaceutical vial. The protective disc shields the end user from sharps injuries and prevents potential contamination of fluid path prior to use. This connector can be packaged separately or in a kit with drug vial and/or syringe. It is compatible with any size syringe (glass or plastic) with a luer tip and can be provided with a silicon-free stainless steel needle (for use with difficult-to-penetrate closures) or with a regular plastic spike.

The VaccJect cartridge-based injection solution provides an alternative to a prefilled syringe, explains Mr. Williams. Fully passive needle retraction is integrated in the device; the needle is never exposed either before or after injection. The drug is contained in a standard ISO cartridge and is kept separate from the device until point of use. This reduces cold-chain shipping and storage costs and eliminates the need for secondary packaging at the pharmaceutical facility.

"VaccJect continues to gain significant market presence with a number of key companies undertaking user studies and clinical trials," says Mr. Williams. "We have developed a partnership with a key pharmaceutical company to offer CMO services to fill 1mL cartridges utilized in the VaccJect with many different drugs."

Mr. Williams says that Duoject is currently developing a new cartridge-based autoinjector and is preparing to launch its new PenPrep Evo reconstitution system to the market in early 2014 with a major pharmaceutical partner. PenPrep Evo offers safe reconstitution between any drug vial and a 1mL or 3mL diluent cartridge. It is used with traditional pen injectors and provides the convenience of a portable discreet device for scheduled multiple self-injections. PenPrep Evo is packaged sterile and is ready for fast reconstitution and maximum recovery of dry form drugs contained in standard vials.

Various configurations of the Unifill syringe, including the Unifill Assure (seen here), are for self injection of viscous biologics.

UNILIFE—ENHANCING INJECTABLE THERAPIES

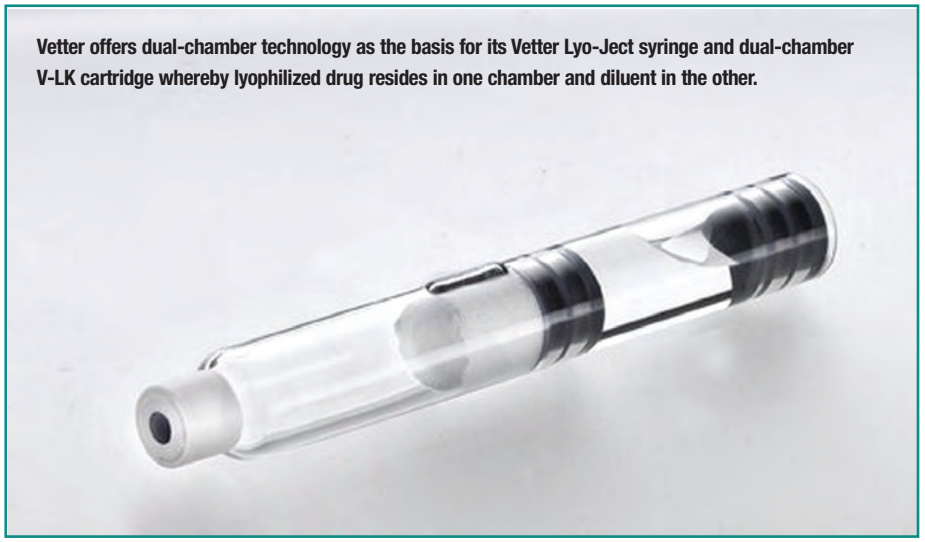
Unilife offers pharmaceutical customers a range of differentiated injectable drug delivery systems: prefilled syringes with integrated safety; disposable and smart auto-injectors with true end-of dose indicators; wearable injectors with modular features that require no terminal sterilization; dual-chamber syringes that enable ventless, orientation-free reconstitution, and minimal steps of use; and intraocular and specialized delivery systems that enhance dose accuracy and precision. "Each of these verified platforms are highly customizable and designed for seamless integration into standard filling and packaging systems with USP-compliant materials in the primary container," says Stephen Allan, Vice President, Marketing and Communications for Unilife. Customers can select from a range of single- or multi-chamber systems with either staked or attachable needles in multiple sizes and lengths.

Considered to be Unilife's flagship product, the Unifill syringe is a ready-to-fill system with automatic and fully integrated safety features. "Human factor studies and other market evaluations with healthcare workers and patients continue to highlight that Unifill is strongly accepted and preferred for use," says Mr. Allan. "Various configurations of the Unifill syringe, including the Unifill Assure for patient self injection of viscous biologics, are regularly supplied to customers."

Additionally, the EZMix dual-chamber system with simple reconstitution boasts minimal steps and automatic, integrated needle retraction. With ventless, orientation-free reconstitution, EZMix has the potential to enable or enhance the delivery of lyophilized, powder filled or liquid-liquid combination therapies.

"Both Unifill and EZMix leverage an automatic and fully integrated needle retraction mechanism that allows users to control the splatter-free withdrawal of the needle directly from the body into the barrel," explains Mr. Allan.

In addition to expanding its portfolio of injectable drug delivery systems, Unilife continues to increase production capacities and its network of verified suppliers in an effort to accommodate the needs of all biologics, injectable drugs, and vaccines.



Vetter offers dual-chamber technology as the basis for its Vetter Lyo-Ject syringe and dual-chamber V-LK cartridge whereby lyophilized drug resides in one chamber and diluent in the other.

"As a customer-centric, patient-centric, and outcomes-focused organization, Unilife addresses existing and emerging market needs for injectable drug delivery," says Mr. Allan.

VETTER—MATCHING DRUGS TO HAND HELD DELIVERY SYSTEMS

Vetter is a contract development and manufacturing organization (CDMO) that specializes in the aseptic manufacturing of syringes, cartridges, and vials. In collaboration with customers, Vetter offers specialized resources from development and clinical supply to commercial production and life cycle management. As a CDMO, the company helps customers pair their drug with a suitable hand held drug delivery device.

"At each stage, product support meets regulatory, client, and patient requirements," explains Peter Soelkner, Managing Director of Vetter Pharma International. "Beyond market considerations, compatibility with related components like rubber stoppers and closure systems, compound stability, degree of siliconization, filtration and sterilization methods, and other factors must be evaluated and addressed."

This past March, Vetter launched its new commercial filling line for pre-sterilized syringes. The line is built with technologies that enhance safety and maximize API yield. The capacity ranges from mid- to large-volume batch sizes, with a maximum filling speed of 800 units per minute and features a reject-and-sample process; automatic spray disinfection system; fully automatic processing of single- and double-bagged tubs; restricted access barrier system (RABS); optimized routing that shortens the distances between the compounding area and filling station; and a track-and-trace system. "The line was created in part as a response to the need for more efficient, flexible filling operations that enhance safety by minimizing human contact with devices and drug," says Mr. Soelkner.

Vetter also offers dual-chamber technology as the basis for its patented Vetter Lyo-Ject syringe and dual-chamber V-LK cartridge. Lyophilized drug resides in one chamber, diluent in the other. The drug is reconstituted prior to administration. The V-LK cartridge can be used with pen systems in single or multiple doses. "Dual-chamber technology provides product differentiation on the market, whether at initial launch or as part of a product lifecycle management strategy, along with market opportunity as the homecare sector grows," he says.

As a CDMO, Vetter must stay ahead of the curve to meet its customers' needs, says Mr. Soelkner. For instance, growing regulatory pressure and higher quality standards are driving the need for ever-safer manufacturing and packaging of hand held drug delivery systems. "At Vetter, we respond by investing in the technologies and processes that increase patient safety. That includes automating production as much as possible to minimize both human error and human contact with drug and devices. We harness quality by design (QbD) and process analytical technology (PAT) to increase process quality, along with track-and-trace technology. Vetter also uses management tools like Six Sigma to not only increase efficiency, but to minimize error."

Staying ahead of the market also means anticipating future challenges, such as those that are being defined by emerging monoclonal antibodies, multivalent vaccines, and recombinant peptides in the biotech and biopharmaceutical fields. "As their complexity increases, so does their sensitivity to environmental conditions and their need for product-specific filling processes."

WEST PHARMACEUTICAL SERVICES—SIMPLIFYING REPEAT INJECTIONS

West has been one of the leaders in drug containment systems for hand held devices, and has supported customers with the development and manufacture of components and systems for injection devices such as insulin pens and autoinjectors. In the past few years, West has focused on collaborating with our partners, as well as developing a range of proprietary systems aimed at meeting unmet market needs. West's focus is on those areas where repeat injections are necessary,

however the company is exploring new areas where injection has not been the typical route of delivery (e.g. asthma, high cholesterol).

The integration of the drug container and the device as part of a complete system has proven critical in ensuring optimal delivery system performance. "West continues to focus on helping our partners understand and optimize the performance and interaction of four key elements of any successful drug delivery system: the drug, the container, the injection system, and the patient. If any one of these elements is not fully understood, then the overall effectiveness of drug delivery may be compromised," says Graham Reynolds, Vice President, Marketing and Innovation, West Pharmaceutical Services.

In the past year, West announced an agreement with Janssen Biotech to develop and commercialize a new self-injection technology, called the SelfDose injector system. The SelfDose injector system offers patients a user-friendly administration system, and offers pharma/biotech companies the option to use this technology with a simplified pathway to the market.

Additionally, a milestone was achieved for the SmartDose electronic patch injector technology, which incorporates a Daikyo Crystal Zenith polymer cartridge. "We have concluded human trials to assess the performance of the system on the body," says Mr. Reynolds. "Understanding the effectiveness of the system to deliver a large volume over a period of time while attached to the body has been a critical part of the evolution of this technology."

The SmartDose electronic patch injector system technology has progressed to the point of validated systems capable of use in human clinical trials. The SmartDose system technology has been designed to meet the packaging and delivery needs of today's biologic drugs. The Crystal Zenith polymer cartridge system enables sensitive drug containment without the need for silicone oil lubrication, while dimensional precision enables effective and repeatable injection performance. Electronic capabilities within the SmartDose system allow for programmable dosing, as well as enabling user feedback and monitoring. West recently announced the receipt of a $20 million payment from a customer for exclusive access to the SmartDose system in a defined therapeutic area.

The SmartDose system technology from West has been designed to meet the packaging and delivery needs of today's biologic drugs.

"Commercialization will be in line with our customers' timelines for their regulatory filings, but we are increasing capacity for commercial quantities," says Mr. Reynolds.

West has also moved forward with the 1.5mL ConfiDose auto-injector system technology, using a customized 1.5mL Crystal Zenith polymer syringe system. The system offers automatic injection of a single dose within a short period of time, and has been designed to be compatible with a range of syringes and viscosities.

And, the SelfDose system has been advanced to the later stages of development and will be ready for clinical studies later in the year. The SelfDose injector system technology offers a simple, manually-activated injection system, compatible with established prefilled syringes. It enables the user to control the rate of injection, and provides needle hiding before and after injection. It has been designed with the needs of patients in mind, particularly those suffering from rheumatoid arthritis or those with limited dexterity.

Ypsomed's disposable UnoPen (left) for insulin will be launched by first customers in 2014. YpsoMate, a disposable, single-use autoinjector for pre-filled 1mL syringes, is being used in several customer clinical studies.

"With all of our technologies, it is important that to have a thorough understanding of the primary container and how it will be sterilized, filled, and handled," says Mr. Reynolds. "Interaction with the drug delivery system is critical, and it is important that the technology is looked at as a single system to ensure effective functionality."

YPSOMED—MEETING PATIENT AND PHARMA NEEDS

Ypsomed is highly focused on self care, specializing in making injections simple and comfortable to be taken at home. However, pharmaceutical customers have varying needs in terms of both the functionality of the injection systems and the costs, depending on the specific drug and its use, as well as the prevalent market conditions in the country concerned. The main indications for Ypsomed self injection devices are diabetes, inflammatory diseases, growth disorders, osteoporosis, and other indications that require self injection devices.

The company has introduced several products to the market to address both the self administrator and the pharmaceutical client. UnoPen is a disposable pen that is well-suited to insulin suppliers who are competing with the major suppliers in established markets, but it is also suitable for administering GLP-1 drugs, as well as parathyroid (PTH), growth (hGH), and fertility hormones (FSH). "The user-friendly and yet economically priced disposable pen is very well accepted by users and is an important marketing tool that allows pharmaceutical customers to clearly set themselves apart from their competitors," says Ian Thompson, Vice President, Business Development, Ypsomed. UnoPen will be launched in 2014.

Ypsomed is also in the process of industrializing YpsoMate, a disposable, single-use autoinjector for pre-filled 1mL syringes made of glass or plastic. The autoinjector is compact and ergonomic to handle. The needle is invisible to the patient, before, during and after use, making it more acceptable to patients and, therefore, resulting in better compliance. The clearly audible clicks during use and a large viewing window, through which the syringe body can be seen, increase patient confidence and safety, and provide confirmation that the full dose has been injected.

"With this development, Ypsomed follows the constantly growing market for drugs in pre-filled syringes," explains Mr. Thompson. Examples include drugs for autoimmune diseases or long-acting drugs that are administered with a fixed dose. YpsoMate is currently undergoing tests as part of several clinical studies.

"An injection device needs to fulfill several expectations: It needs to be unique and stand out in the market, and at the same time it needs to be affordable in terms of customization costs and cost of goods," says Mr. Thompson. "Furthermore, the development process needs to be fast and without carrying any risk. The production concept should be flexible in a way to support small volumes during Phase 3 and product launch but also capable to produce high annual demands in the commercial phase. Above all the device needs to be easy to use, safe, and effective for the patient."

ZOGENIX TECHNOLOGIES—DELIVERING VOLUMES OF 1ML AND BEYOND

As a developer and marketer of its own pharmaceutical products, Zogenix also offers drug delivery technologies. In 2012, Zogenix partnered with R&D experts at

Battelle to offer the DosePro instantaneous, needle-free delivery system to other pharmaceutical companies. There are two big stories that emit from the Zogenix/Battelle partnership. "The first is evidence confirming that the integrity of biomolecules such as monoclonal antibodies is maintained upon instantaneous, needle-free delivery via our DosePro technology," says John Turanin, Vice President and General Manager, Zogenix Technologies. Battelle and Zogenix conducted an *in vitro* study showing that the integrity of Humira (AbbVie) delivery by DosePro is no different than PFS controls. In addition, MedImmune and Zogenix co-authored two posters at the AAPS National Biotechnology Conference in May 2013: The first study comparing delivery of two monoclonal antibodies by DosePro and PFS controls, and the second assessing delivery of model viscous formulations, mimicking those for mAbs. "Both of these studies demonstrate positive results for DosePro delivery of biomolecules and their typical viscous formulations," he says.

The second story is that the availability of a needle-free self-injection option in rheumatoid arthritis could result in a 30% increase in patients' willingness to accept a prescription for a drug requiring self-injection, with considerable preference for needle-free instantaneous delivery over traditional injection alternatives such as pre-filled syringes and standard autoinjectors, continues Mr. Turanin. "This was a key finding in a 300-patient survey presented at AAPS NBC in May."

The DosePro is a prefilled, single-use subcutaneous injection technology designed specifically to overcome the barriers for adoption of and adherence to prescription for self-injectable drug products. This is accomplished by calming the natural human "flight" response when faced with the idea of inserting a sharp metal rod into one's body; by offering extremely simple user interface options; and completing the dose in less than 1/10th of a second vs. the usual 10-15 seconds for standard autoinjectors, explains Mr. Turanin. "In addition, the fundamentals of the technology make the issue of formulation viscosity "irrelevant," i.e., *in vitro* studies demonstrate that DosePro can deliver viscous formulations in 100s cP without degrading the 1/10th second delivery time or dose accuracy, a feat unachievable with standard autoinjectors."

The applicability of the DosePro technology for subcutaneous delivery ranges from drugs that are small molecules to biomolecules, stable in aqueous formulation or suspension, and with a fixed dose that is a single prefilled, fixed, bolus.

DosePro has achieved commercial drug status, having been approved by FDA (2009) within its first drug/device combination product, SumavelDosePro (sumatriptan for injection) and launched in 2010, followed by EU approvals in 2010. A key commercial manufacturing milestone was recently achieved with the release to market of the 2 millionth SumavelDosePro.

Zogenix maintains two areas of focus. One is to ensure that biopharmaceutical companies have the opportunity to assess for themselves the application of our technology for biologics targeting autoimmune disorders such as rheumatoid arthritis. Within Battelle's laboratories, Zogenix has established a Center of Excellence that can perform in vitro evaluations of biomolecules. The second area of focus is a technology extension program to expand the volume of the dose instantaneously delivered by the DosePro system from 0.5mL to 1mL and beyond.

"We have only scratched the surface of the potential applications for the DosePro technology," says Mr. Turanin. "The future lies in expanding the applications to the hundreds of subcutaneously administered biologics that are in development pipelines and for providing sustainable competitive differentiation for those already on the market for life-cycle extension. With the increase in dose volume under development, the DosePro technology should have broad applicability for years. The intention of the Zogenix and Battelle partnership is to license the technology to select biopharmaceutical partners with strategic drug candidates in key classes and target therapeutic areas." ◆

REFERENCE

1. Datamonitor, PharmaVitae Explorer, January 2012.

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Technology & Services Showcase

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Licensing & Capabilities

Aveva has a number of products for license from its development pipeline along with a full complement of R&D capabilities to produce transdermal drug delivery systems that fortify pipelines and maximize product life cycles. Aveva Drug Delivery Systems is one of the world's largest manufacturers of, and a pioneer in, transdermal drug delivery systems with a rich history of providing pharmaceutical partners with fully integrated, controlled-release transdermal products that fulfill unmet market needs. Products for licensing include Sufentanil, Fentanyl, Clonidine, and Nicotine. For more information, contact Robert Bloder, VP of Business Development, at (954) 624-1374 or visit **www.avevadds.com**.

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Technology & Services Showcase

Biologics Development

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Technology & Services Showcase

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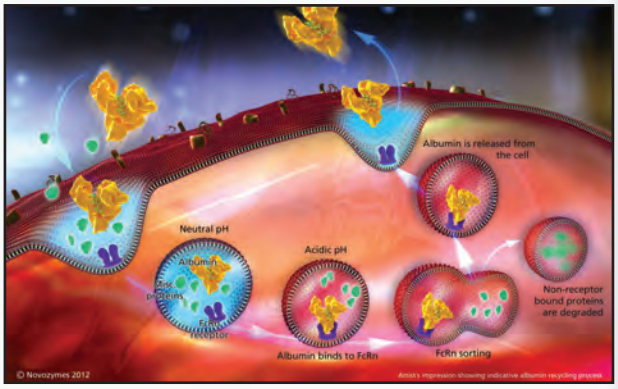
Tunable Half-Life Extension Technology



Novozymes' tunable half-life extension (HLE) technology can flexibly extend half-life to reduce the dosing frequency of drugs from days to weeks. Based on albumin, Novozymes offers HLE by genetic fusion, Albufuse® Flex, or chemical conjugation, Recombumin® Flex, enabling the tunability of HLE to meet the needs of a specific disease or application. Leading the way in improving patient quality of life, Novozymes' technology is already being widely used in the fields of diabetes, haemophilia, and neutropenia. Through the optimization of drug half-life, dosing frequency and healthcare costs can be reduced while increasing patient compliance. Long patents until at least 2030 also provide manufacturers with a unique competitive edge in current challenging markets. For more information on Novozymes' HLE technology, please visit **www.halflifeextension.com.**

Technology & Services Showcase

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DRUG DEVELOPMENT
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CAPSUGEL DFS: INTEGRATING TECHNOLOGY FOR INNOVATIVE FINISHED DOSAGE FORMS

Amit Patel
President,
Dosage Form Solutions,
Capsugel

"Our encapsulation and liquid fill technology expertise is being leveraged for unparalleled speed and precision in formulation development and manufacturing."

With the push to bring new drugs to market faster, the healthcare industry has made significant advances in utilizing liquid and semi-solid fill technology, and incorporating lipid-based drug delivery systems to expedite development. While lipid-based formulations have proven to be capable of addressing bioavailability, high active pharmaceutical ingredient (API) potency, low dosing levels, and stability challenges, many formulation challenges still remain. With a very high proportion of the industry's development pipeline consisting of molecules with poor bioavailability, advances in lipid-based formulation technologies are essential to the future of drug development. Amit Patel, President of Capsugel's Dosage Form Solutions (DFS) business unit, speaks to Drug Development & Delivery about the formulation challenges facing the industry and the increasing pressure on companies to innovate and accelerate speed from lab-to-clinic and clinic-to-commercial to remain competitive in today's dynamic marketplace.

Q: Can you provide our readers with some background on industry challenges related to formulations and what action Capsugel has taken to address them?

A: Two primary, high-level challenges come to mind. First, nutritional and pharmaceutical product companies are constantly seeking ways to bring improved products to the market. "Improvement" can mean a number of things – enhanced bioavailability and absorption, optimized active ingredient dosing for highly potent compounds, improved stability, and even taste- and odor-masking, amongst others. Second, companies are interested in accelerating the speed from lab-to-clinic and from clinic-to-commercial.

Capsugel's new Dosage Form Solutions (DFS) business unit was created to fully leverage

our encapsulation leadership, especially in liquid fill, to help address some of our customers' most pressing challenges for existing and new nutritional and pharmaceutical products. DFS integrates various areas of Capsugel expertise – proprietary technology platforms, formulation R&D centers, and finished dosage commercial manufacturing sites – to work with customers to develop more innovative products. For example, the LIPIDEX platform integrates recently acquired Encap Drug Delivery and consolidates our leadership in liquid fill, giving us an additional FDA accredited manufacturing site and specific technologies in capsule banding, sealing, and coating. Some aspects of our proprietary platforms, taking a liquid fill approach to solid oral formulations, or having targeted release functionality as being intrinsic to the capsule shell (rather than applied through a coating), are naturally suited to help improve time-to-market because the approaches eliminate numerous time-consuming or technically challenging development steps.

Our premier capability in encapsulation in a vertically integrated B2B model allows us to partner with customers throughout the formulation process, clinical evaluation, and manufacturing of encapsulated dosage forms. We also leverage our specialized capabilities in polymer science, equipment design, and process engineering to help our customers develop better products faster, in an integrated and focused manner.

Q: Given the increasingly dynamic marketplace, companies are trying to carve out specialist positioning. Where are the emerging opportunities for drug development companies?

A: It is a very "dynamic" marketplace, due not only to multiple recent acquisition transactions, but also to other factors, including evolving customer preferences, changing regulatory landscapes, technology advances, and new emerging business models. The pharmaceutical customer is facing tremendous pressure in bringing small and large molecules to market and increasingly needs specialist partners. Such partners need to determine what their best value proposition is for the industry – how can they best meet marketplace and customer demands. DFS is currently focused on liquid fill, inclusive of lipid and semi-solid, as well as targeted release technologies.

What differentiates Capsugel from other companies that align themselves with traditional roles such as CRO, CMO, or CDMO is robust intellectual property (IP). Capsugel DFS has an extensive IP estate surrounding our encapsulation technology platforms, as well as select internally funded finished dosage products that we are developing for subsequent marketing by licensed partners. We focus on leveraging our specific depth in liquid fill and lipid formulation expertise, as well as tailoring the hard capsule shell for modifying release. Our expertise in these technology platforms is premier in the industry.

Q: Do you see bio-enhancement remaining as a primary formulation challenge for the drug delivery industry?

A: There are numerous industry challenges. Bio-enhancement is one of many. Other formulation challenges include API potency, low dosing levels, and stability problems. Determining how best to meet these formulation challenges is paramount to the success of the industry. Without continued innovation, new or improved products will not be developed. I believe significant opportunity exists in two key areas:

(1) Bioavailability from a formulation and commercial viability standpoint and;

(2) Speed of formulation development and evaluation.

Today, up to 90% of new chemical entities in development are said to fall under either Biopharmaceutics Classification System (BCS) Class II or Class IV. Specifically, the bioavailability of the vast majority of drug candidates is expected to be low. There are a variety of different approaches utilized to improve solubility, often dependent upon the companies' experience, to bring the bioavailability to an efficacious level and take these products to market.

Similar to solid dispersion approaches, lipid-based formulations can address a wide range of bioavailability challenges and are therefore utilized in the decision trees of many companies. However, formulators often seek deep technical assistance in identifying and developing an

optimal bio-enhanced formulation, e.g. a lipid-based solution, suspension, or SEDDS/SMEDDS. To meet this demand, DFS has pulled together Capsugel's collective historical capabilities and experience in lipid-based applications and approaches.

Capsugel has invested heavily throughout the past decade in lipid technology development with more than 400 reference formulations developed and a multitude of products brought to market. This experience has facilitated the development of a proprietary lipid expert system that is core to our fast-to-clinic program.

Our established fast-to-clinic program can complete preformulation work in five weeks and then move through formulation evaluation and dosage form selection, leveraging the liquid fill expert system where applicable, in an additional 15 weeks. Our encapsulation and liquid fill expertise is being leveraged for unparalleled speed and precision in formulation development and manufacturing.

Specialized equipment has been developed for capsule filling and sealing at clinical scale (CFS 1500), as well as commercial scale (LEMS 70), further facilitating clinical evaluation, ease, and predictability of scale-up while optimizing commercial manufacturing.

Q: Let's talk about 505(b)2 filings – what role will they play in driving industry growth?

A: New Drug Applications (NDAs) based on 505(b)2 filings are likely to continue to be an industry growth driver. Developing a New Chemical Entity (NCE) requires significant time and resources (as long as a decade, and, at times, upward of a billion dollars per successful NCE). Additionally, the rate of commercialization success for small molecules is low, partially due to the bioavailability challenge previously referenced. Therefore, it is prudent for the industry to be pursuing new indications and improved target product profiles based on existing APIs.

The 505(b)2 NDA proposes a limited change to a previously approved product while demonstrating the required efficacy and safety of the change. Cost-value for the FDA 505(b)2 application is the avoidance of time-consuming, costly, and sometimes repetitive preclinical and clinical trials.

Further, revenue-value for the 505(b)2 can be extensive, offering the sponsor with three to five years of market exclusivity dependent upon the extent of change against the innovator product, as well as potential for exclusivity driven by intellectual property. Contrast this with only 180 days of exclusivity for an ANDA (and that for only successful first-to-file Paragraph IV filings), and it's easy to see why there is increased pursuit of 505(b)2 approvals.

Q: What are the technology platforms Capsugel offers to address industry challenges of NCE and 505(b)2 development?

A: Unveiled in June, our new LIPIDEX® technology platform provides customers a comprehensive lipid, liquid, and semi-solid fill offering unique in the industry. LIPIDEX consolidates the breadth of lipid technologies developed by Capsugel, its extensive R&D formulation background, and liquid/semi-solid fill commercial manufacturing capability.

We have been formulating with lipids for many years with extensive project experience in meeting a myriad of formulation challenges – solubility, permeability, dose uniformity, low dose/high potency issues, food effect – as well as reformulating from non-oral dosage forms to liquid fill encapsulation. Improving solubility can facilitate smaller, more efficient dosage forms, as well as format changes. More efficient targeted release, our other area of focused investment, can also facilitate improved bioavailability as well as large molecule reformulation to solid oral dose.

We bring options and flexibility to pharmaceutical formulators and commercial teams. Our dosage form options include SGcaps® soft gelatin capsules and Licaps® liquid filled capsules. Capsugel continues to innovate and expand its lipid-based technology. A new solid lipid pellet dosage form is currently being used in both internal and client product

development and is anticipated to launch in the coming months.

Our research and development capabilities are built around three state-of-the-art R&D centers located strategically in the United States and Europe. Collectively, these teams in Cambridge, MA, Strasbourg, France, and Livingston, Scotland, have over 20 years of focused formulation development experience for pharmaceutical and nutraceutical applications. These teams utilize a fast track evaluation protocol incorporating expert systems. Our formulation scientists have extensive background in simple to complex lipid systems in solution, suspension, or SEDDS/SMEDDS formulations. Small-scale liquid fill manufacturing technology is also available at our R&D locations.

Commercial manufacturing rounds out the LIPIDEX technology platform. We have liquid/semi-solid fill manufacturing in the United States, United Kingdom, France, and Japan. We have FDA- and MHRA-accredited finished dosage form manufacturing sites as well as high containment capability, hormone and controlled substance manufacturing, and modified release applications.

Q: With the industry's focus on speed to market, does it make strategic sense for companies to seek formulation or development partners earlier in the development process no matter what challenges the compound may have?

A: Absolutely. In today's competitive development environment, companies should seek collaborations with specialist companies possessing deep science and engineering capabilities in key technologies early in the development process. We believe that such early involvement maximizes the value-add we can bring our partners, eliminating or minimizing a costly trial-and-error formulation approach.

Q: As you look ahead, what industry trends beyond lipid-based drug delivery are on the horizon for the industry?

A: There are several emerging areas in the industry that we are addressing, but the following two in particular come to mind: (1) Targeted drug delivery systems and (2) Abuse-resistance technology.

With the recent acquisition of Encap Drug Delivery, our formulation teams are looking ahead toward further development of our targeted drug delivery systems. Effective targeted delivery, inclusive of more consistent release at a targeted pH dissolution point, is important in improving the bioavailability and efficacy of the drug.

Encap's dual release technology (DUOCAP) and Colonic Delivery Technology (ENCODE) are being integrated with our dual release approaches and DRcaps® acid-resistant technology. Our capsule coating capability, utilized for both controlled and targeted release applications, gives us additional flexibility in tailoring dissolution profiles and/or facilitating dual drug release where needed to meet a target product profile. We will soon launch an intrinsically enteric capsule for the pharmaceutical segment, positioned for rapid clinical evaluation without time-consuming tablet and enteric coating preparation and application steps. We believe that the enteric capsule will have further applications in large molecule delivery, and additional applications in conjunction with liquid fill formulations.

Another area of growth for Capsugel DFS is abuse resistance – especially noteworthy given the recent US FDA ruling preventing generic oxycodone products coming to market without abuse resistance. We have multiple projects underway, some customer-sponsored and some internally funded, that are leveraging our experience with abuse deterrence formulations and ABUSOLVE technology platform.

In summary, Capsugel will continue to apply and expand our offering in bio-enhancement and specialized drug formulation to remain at the forefront of this rapidly evolving industry. ◆

New Therapeutics for Aggressive Brain Cancers

By: Jeffrey Bacha, MBA

INTRODUCTION

In May 2008, Senator Ted Kennedy suffered a seizure, prompting a quick visit to local Cape Cod Hospital, immediately followed by a medical helicopter flight to Massachusetts General Hospital.[1] A few days later, on May 20, 2008, doctors reported that a brain tumor caused the seizure. Subsequent biopsy of the tumor tissue revealed that Senator Kennedy had malignant glioma of the parietal lobe. He passed away from the brain tumor 15 months later on August 25, 2009, at his home. The next morning, an NBC headline read: "Kennedy's tumor was aggressive and deadly. After suffering a seizure last year, the senator battled a malignant glioma."

Indeed the headlines were apt as Senator Kennedy was killed by the most aggressive type of malignant glioma, namely glioblastoma multiforme (GBM) - also one of the deadliest tumors in humans. Even today, despite maximum treatments available, patients still only have median survival times of 15 months. And left untreated, patients will likely succumb to this type of brain cancer in just a few months.

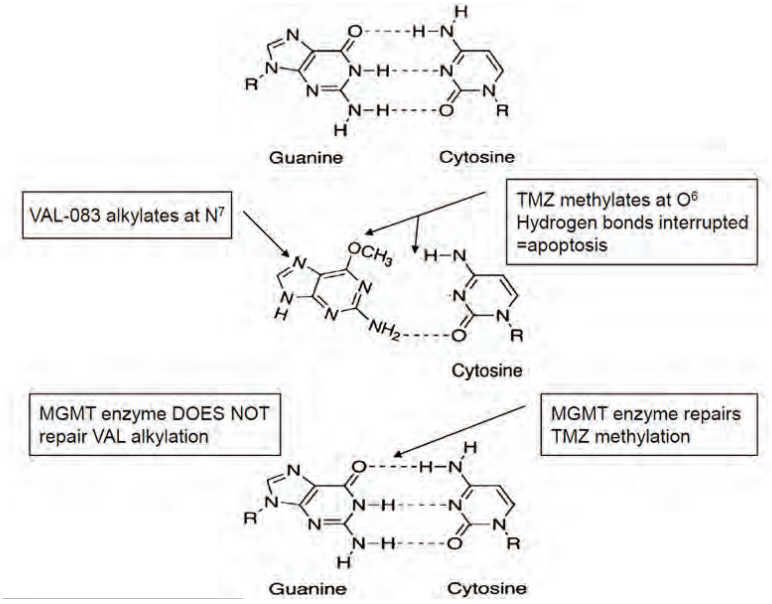
GBM ACCOUNTS FOR MORE THAN HALF OF ALL GLIOMAS

In the US, an estimated 15,000 people have glioblastoma. Of the 25,000 malignant brain tumors diagnosed annually, glioblastoma represents approximately 70%. Gliomas are brain tumors that arise from glial cells, namely astrocytes in GBM, which comprise the supportive "glue-like" tissue of the brain, and they account for over 30% of all primary brain and central nervous system (CNS) tumors diagnosed in the US. GBM is the most malignant and most common, accounting for more than half of all gliomas.

An effective treatment for glioblastoma is needed. Patients with GBM have a median survival of 14.6 months and an overall survival of only 10% at 5 years, even after standard of care (SOC) treatment: surgery, ionizing radiation (IR), and the alkylating chemotherapeutic temozolomide (Temodar®).[3]

Further, many GBMs have or develop resistance to alkylating chemotherapeutic agents. And while the more recent addition of Temodar (in the mid-2000s) to surgery and radiation therapy has improved survival rates of patients alive after 2 years - from about 10% to 26% - the prognosis today is still grim for glioblastoma.[2]

FIGURE 1



VAL-083: MGMT-Independent MOA
Temodar resistance is caused in part through cleavage of the methyl adduct formed by Temodar, which is thought to occur by the enzyme, O6-methylguanine-DNA methyltransferase (MGMT). Forming DNA adducts that are not repaired by MGMT can be accomplished using VAL-083, a novel agent that causes N7 adducts.

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RESISTANCE IS A MAJOR PROBLEM WITH TODAY'S STANDARD OF CARE

Generally, tumors of the brain are the most challenging malignancies to treat. Current treatments tend to be aggressive and multifarious. Further, many studies report several determinants of resistance to the current standard of care, such as: (1) O6-methylguanine-DNA methyltransferase (MGMT) expression, (2) the complexity of several altered signaling pathways in GBM, (3) the existence of glioma stem-like cells (GSCs), and (4) the blood-brain barrier.[3,4,5,6]

Newly diagnosed patients suffering from glioblastoma are initially treated through invasive brain surgery, although disease progression following surgical resection is nearly 100%. Due to the extreme challenge presented to surgeons by these tumors, which can morphologically appear as necrotic hemorrhagic infiltrating masses, and the critical nature of surrounding brain tissue, taking wide margins to include healthy tissue as sometimes is done with other cancers is almost impossible. Thus obtaining clear margins is highly improbable.

Temodar in combination with radiation is the front-line therapy for GBM following surgery. Temodar currently generates more than $950 million annually in global revenues primarily from the treatment of brain cancer. Yet approximately 60% of GBM patients treated with Temodar experience tumor progression within 1 year. This may be due to resistance of the tumors to Temodar, an alkylating chemotherapeutic, especially in those tumor cells that express high levels of MGMT.

MGMT EXPRESSION CAUSES GBM RESISTANCE TO SOME ALKYLATING AGENTS

Many glioblastomas have or develop resistance to alkylating chemotherapeutic agents such as Temodar. One common mechanism of such resistance is mediated by the repair enzyme O6-methylguanine-DNA methyltransferase (MGMT), which is capable of counteracting the anti-cancer cytotoxicity induced by O6-alkylating agents.[2] Further, increased MGMT expression is well correlated with in vitro and in vivo glioma resistance to Temodar.[4]

One potential strategy studied for overcoming this resistance is simply administering more frequent Temodar doses in what are referred to as dose-dense or dose-intense schedules; however, this has resulted in little benefit in the clinical setting.[5] Another strategy is direct enzyme inhibition using O6-benzylguanine, which has been studied in combination with Temodar, but did not yield substantial benefit clinically.[6] Therefore, selecting alternate chemotherapeutic agents whose cytotoxic mechanisms are not subject to this MGMT resistance, such as VAL-083 (dihydrogalactitol), may prove to be most beneficial for treatment (Figure 1).

TREATMENT WITH AVASTIN® TARGETING ALTERED VEGF SIGNALING PATHWAY IN PATIENTS FAILING TEMODAR

GBM is characterized by sustained angiogenesis - the key regulator of which is vascular endothelial growth factor (VEGF).[4] Bevacizumab (Avastin, BEV) is a humanized monoclonal antibody that binds to and inhibits VEGF. In 2009, the FDA granted approval to bevacizumab injection as a single agent for patients with glioblastoma, with progressive disease following prior therapy.

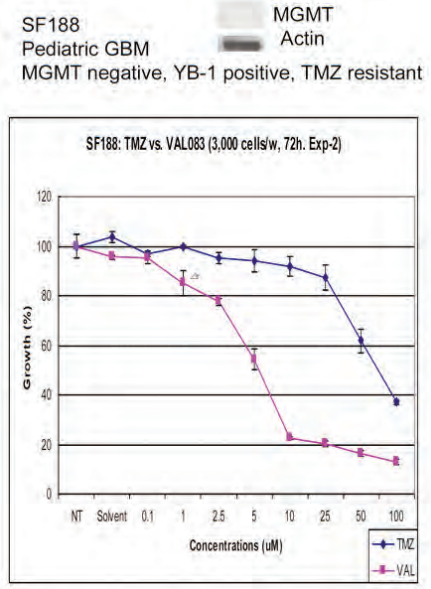
According to the Avastin label, approximately 20% of patients failing Temodar respond to Avastin therapy. Even with a relatively small patient population, the market for this treatment until recently is still quite large, and analysts anticipate annual Avastin revenues for the treatment of brain cancer may reach $650 million by 2016. Yet interestingly, the Avastin package insert also states that effectiveness in glioblastoma indication is based on improvement in objective response rate - in this case, based both on WHO radiographic criteria and by stable or decreasing corticosteroid use. Further, the label also provides, "No data available demonstrating improvement in disease related symptoms or survival with Avastin."

In fact, new data from two additional clinical trials on the use of Avastin in glioblastoma presented recently at the annual American Society of Clinical Oncology (ASCO) reveal that Avastin is not a safe or effective choice as a first-line treatment in this indication. And overall Avastin was shown not to have benefit in GBM.

In both studies, Avastin did have a significant impact on progression-free survival (PFS) endpoints, yet it had no impact on overall survival (OS).[7] In addition, according to some researchers, using PFS as a primary endpoint is controversial, particularly in patients treated with antiangiogenic therapies (such as bevacizumab) that can lead to improved imaging findings without actual tumor response (a so-called pseudoresponse).[4] Also in one study, there was an increase in grade 3 or higher adverse effects in the Avastin arm, including neutropenia, hypertension, and deep vein thrombosis/pulmonary embolism.[7]

So, as has happened in other indications, such as breast cancer, Avastin is clearly affecting the tumor, but this does not translate to a survival benefit. Approximately 48% of patients who are diagnosed with GBM will fail both front-line therapy and Avastin. Thus, it is clear that new therapeutics are needed to improve the treatment options for patients with glioblastoma, both in first-line and recurrent treatments.

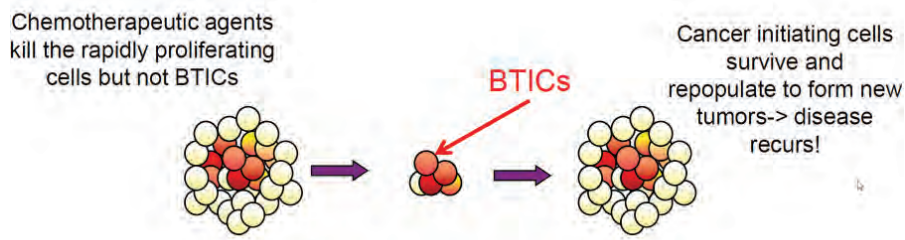
FIGURE 2



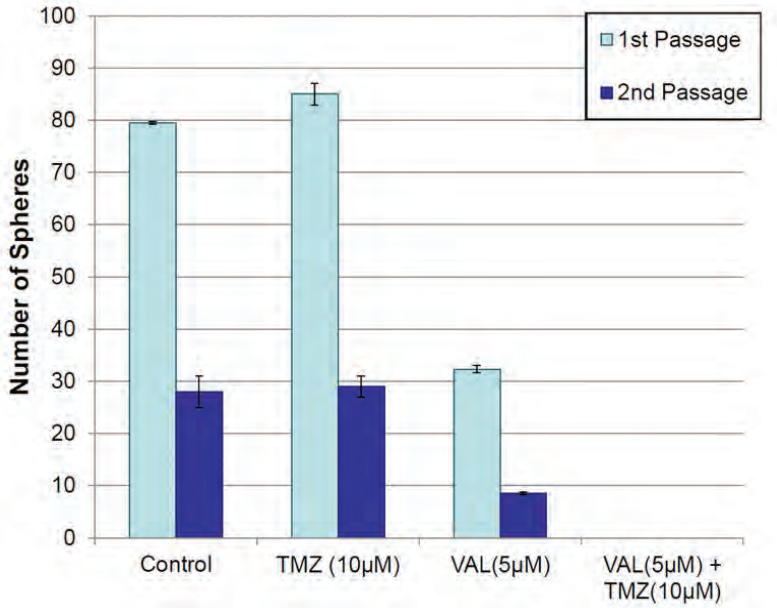
VAL-083 Effectively Inhibits Tumor Cell Growth
VAL-083 was better than Temodar for inhibiting growth of adult Glioblastoma tumor cells (U251, T98G) in an MGMT-independent manner (Data not shown in this graph, AACR poster). Pediatric Glioblastoma cells (SF188) are insensitive to Temodar through an MGMT-independent mechanism, however; they are sensitive to VAL-083.

FIGURE 3A & 3B

A



B



VAL-083 is Active Against Glioma Stem Cells
Brain-tumor-initiating cells are thought to give rise to relapse as they are resistant to conventional therapies. Using a self-renewal assay, VAL-083 was shown to inhibit growth of SF188 cells in this assay.

NEW THERAPEUTIC APPROACHES SHOW PROMISE TO TREAT GLIOBLASTOMA

Vaccines & Immunotherapeutic Approaches

Immunotherapy is a promising alternative to conventional treatment for glioblastoma and includes active and passive strategies. Active immunotherapy upregulates an immune response to tumor and can confer long-term immunity that potentially continues to provide protection against future tumor recurrence. Passive immunotherapy involves the transfer of immune effectors to achieve an immediate effect but does not generate long-term immunity.[2]

Active Immunity: Peptide vaccines seek to induce the immune system to generate a response against the tumor. Of particular interest is a peptide vaccine, known as rindopepimut (CDX-110, Celldex Therapeutics), targeted at epidermal growth-factor receptor variant III (EGFRvIII). This is one of the few identified truly tumor-specific antigens.[2] CDX-110 vaccine is currently in several advanced of clinical trials in combination with RT and Temodar.

In particular, CDX-110 is being studied in patients with newly diagnosed tumors that contain the mutation in question in which population it has shown positive results in a Phase II study. It is reported that about 30% of the population has such a variant. Several other promising tumor vaccine strategies are also being used in clinical trials.

Dendritic cells, the immune systems most potent antigen-presenting cells, can be primed with tumor antigen ex vivo and readministered to the patient, where they mediate T-cell activation.[8] Numerous preclinical studies demonstrate that dendritic cells pulsed with glioma antigens can prime a cytotoxic lymphocyte response that is tumor specific.[2] Thus, immunotherapy with dendritic cells potentially offers high tumor-specific toxicity with sustained tumoricidal activity.[9]

Of particular interest is a multi-epitope-pulsed dendritic cell vaccine, namely ICT-107, being developed by researchers at Cedars Sinai Medical Center.[8] The vaccine targets six antigens (HER2/neu, TRP-2, gp100, MAGE-1, IL13Rα2, and AIM-2) involved in the development of glioblastoma cells. Findings from a Phase I clinical trial yielded many interesting results. First, overall survival was 38.4 months, significantly longer than the typical 14.6-month survival of patients with newly diagnosed glioblastoma receiving standard therapy alone, which includes radiation and chemotherapy. Second, patients with tumors that expressed large amounts of MAGE-1, AIM-2, gp100, and HER2 had better immune responses and longer progression-free survival rates, suggesting that these antigens may be particularly vulnerable to the vaccine.

Researchers also reported finding evidence that ICT-107 attacks some brain cancer stem cells, considered by many to be the original source of tumor cells. These self-renewing cells appear to enable tumors to resist radiation and chemotherapy and even regenerate after treatment. Thus, cancer stem cells are especially appealing targets: killing the stem cells is believed to improve the chances of destroying a tumor and preventing its recurrence. With these encouraging results a Phase II trial is underway.[9]

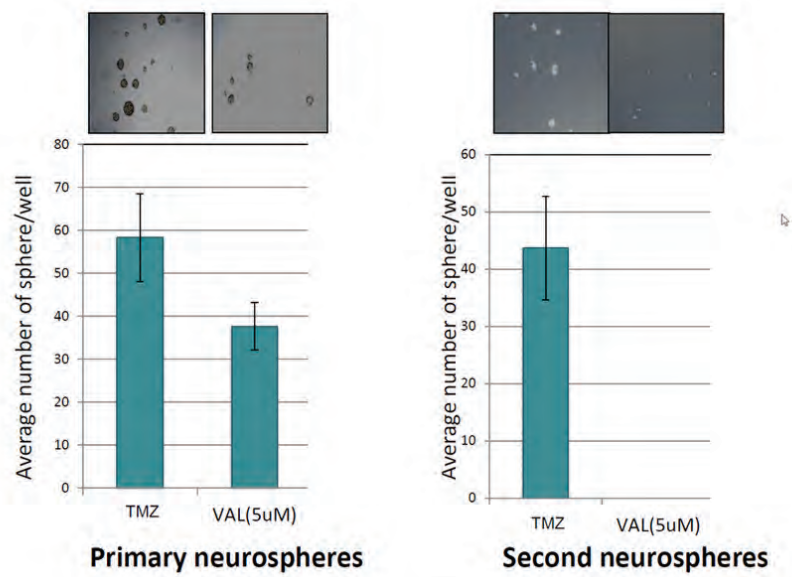
Passive Immunity: Antibody-mediated drug delivery serves a dual purpose of increasing the local drug concentration while minimizing systemic exposure. Antibody drug conjugates have been developed that couple monoclonal antibodies targeting glioma-specific structures to radionuclides (radioimmunoconjugates), exotoxins (immunotoxins), or chemotherapeutic agents and are administrated locally. Antigens that are overexpressed in tumors relative to normal

tissue are typically used, such as mutant EGFR, IL-4 or IL-13 receptors.[2]

Although the benefits of immunotherapy are becoming evident, here and in other fields, substantial breakthroughs supporting its use as the standard-of-care treatment for GBM have yet to be realized. In general, tumors of the CNS pose a distinct set of challenges that may limit the ability to generate an optimal antitumor immune response. Some of these factors include:

- A tight blood-brain barrier that may interfere with localization of immune effectors into the CNS
- Profound immune suppression due to immunoregulatory factors secreted by tumor cells
- A lack of well-defined, tumor-specific antigens for GBM.[10]

FIGURE 4



VAL-083 is Active Against Temodar-Resistant Brain Cancer Stem Cells
VAL-083 inhibits the growth of Temodar-resistant BT74 cells, a brain-tumor-initiating cell line. VAL-083 completely inhibits neurosphere formation.

NEW METHODS FOR LOCAL DRUG DELIVERY TO BYPASS BLOOD BRAIN BARRIER

One of the major challenges of chemotherapy for GBM is the achievement of adequate drug concentration within the tumor itself. The blood-brain barrier, although often weakened in areas of bulky tumor, still acts as a barrier against many drugs, particularly in the periphery of the tumor, which is often highly infiltrative.[2] The blood-brain barrier is designed to protect the CNS and blocks most anti-cancer drugs, especially molecules that are larger than ~500 Da. Many drugs are denied access to the very regions where they would be effective, thus limiting the clinical application of most anti-cancer drugs for treating brain tumors

So novel methods, such as "superselective intra-arterial cranial infusion" employing microcatheters that when inserted in the groin can be threaded up through tiny vessels almost anywhere in the brain to spray extraordinarily high doses of drugs (some in initial procedures used Avastin) straight to tumors or areas of resection without soaking the rest of the brain in the particular drug and further exposing it, which often results in nasty side effects. For such a procedure, mannitol is first delivered to open up the blood-brain barrier temporarily in order to get chemotherapy in the brain.[11] Basically, mannitol pulls water out of the tightly packed cells lining brain capillaries so they shrink and pull away from one another, opening gaps through which drug molecules can pass into the brain tissue. And then the selected drug, in certain studies, Avastin can advance directly to the tumor.

Another novel delivery system utilizes a concept called convection-enhanced delivery, in which surgeons implant one or more catheters into the tumor and the surrounding brain.[12] Other chemotherapeutic agents (such as in one particular study with topotecan) are slowly pumped directly into the tumor and surrounding tissue over the course of a few days (e.g. 4 days). Because convection-enhanced delivery is done so slowly, the agent can accumulate in very high concentrations in the tumor, allowing physicians to achieve drug levels more than a thousand-fold greater than is possible with intravenous delivery. Because topotecan is a topoisomerase inhibitor, it affects only multiplying cells such as those in tumors and does not create any additional side effects.

New Cytotoxic Approach with MGMT-Independent Mechanism of Action

DelMar Pharmaceuticals has initiated human clinical trials to develop a novel small drug candidate, VAL-083, a chemotherapeutic, that employs a different mechanism of action than presently used chemotherapeutics, such as alkylating agent Temodar. In particular, VAL-083 employs a mechanism of action seemingly unaffected by MGMT enzyme expression. The enzyme expression triggers the DNA cell repair mechanism that counteracts the cytotoxic activity of currently employed chemotherapeutics, thus leading to the tumor resistance, which occurs in more than half the GBM patient population. Therefore, VAL-083 effectively addresses the problem of MGMT-related tumor resistance.

Specifically, VAL-083, as a first-in-class small-molecule chemotherapeutic, has a molecular structure that is not an analogue or derivative of other small molecule chemotherapeutics approved for the treatment of cancer. VAL-083 has been previously assessed in multiple (>40) clinical studies sponsored by the National Cancer Institute (NCI) in the US as a treatment against various cancers, including lung, brain, cervical, ovarian tumors, and leukemia.

Shelved by the NCI, while other drugs and more complex biologic treatments were pursued a number of years ago in the initial front to the war on cancer, VAL-083 was overlooked, until recently. With such a large amount of clinical data available for VAL-083, it has historical and established proven validity in battling cancer. In fact, published preclinical and clinical data suggest that VAL-083 may be active against a range of tumor types. Additionally, VAL-083 is approved as a cancer chemotherapeutic in China for the treatment of

chronic myelogenous leukemia (CML) and lung cancer. VAL-083 has not been approved for any indications outside of China.

More recently, in October 2011, DelMar Pharmaceuticals initiated clinical trials with VAL-083 as a potential new treatment for GBM. In April 2012, data presented at the American Association of Cancer Research (AACR) annual meeting demonstrated that VAL-083, as expected, maintains activity in tumors resistant to the current front-line GBM therapy, Temodar, due to MGMT-related chemo-resistance (Figure 2). Currently, there is no approved therapy for these patients. DelMar's data also suggests that VAL-083 is active against glioma stem cells (GSCs) that are resistant to standard chemotherapy (Figures 3 and 4). Further, VAL-083 is safe and well tolerated at doses tested to date.

In November 2012, interim data from a clinical trial was presented at the Annual Meeting of the Society for NeuroOncology (SNO) demonstrating that VAL-083 can shrink or halt the growth of tumors in brain cancer patients who have failed other approved treatments. Most recently, reports continue to confirm the findings of previous studies and potentially position DelMar for advancement to registration trials in early 2014.

Specifically, VAL-083 Phase I/II clinical trial interim results that were presented at AACR and ASCO 2013 indicate the following:

- VAL-083 is safe and well tolerated at doses tested to date
- A portion of patients tumors were observed to shrink or stop growing following initiation of treatment
- Benefits were seen in both glioblastoma and in other cancers that have spread to the brain
- Doses to date are lower than NCI-regimen, indicating potential for an improved dosing regimen and side effect profile
- Plasma exposure observed to increase in accordance with dose.

With a potential improved dosing regimen and side-effect profile in combination with the ability to treat patients with MGMT-resistant tumors, clinical trial data for VAL-083 is encouraging for this new chemotherapeutic in development to treat glioblastoma.

NEW THERAPIES TO TREAT GLIOBLASTOMA ARE URGENTLY NEEDED

As we have reviewed, glioblastoma is one of the most common and fatal brain cancers, and new therapies to treat this disease are urgently needed. New approaches, such as vaccines and immunotherapies, have promising results, and to be most effective, will need to be used in combination with a chemotherapeutic, such as VAL-083. Thus, VAL-083 provides a promising and effective strategy for new single and combination therapies for GBM and other cancers.

With about 15,000 patients with glioblastoma in the US alone, there is clearly an unmet need for more effective therapies. In particular, therapies are needed that can further extend the life span of patients diagnosed with this disease, significantly improve the overall quality of their extended survival time, and ultimately, in coordination with adjunctive therapies, aim to provide a cure. ◆

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BIOGRAPHY

Jeffrey Bacha is a seasoned executive leader with nearly 20 years of life sciences experience in the areas of operations, strategy, and finance. He is currently president, CEO, and co-founder of DelMar Pharmacueticals and serves as a director of Sernova Corp. Prior to this, he was the founding CEO of Inimex Pharmaceuticals Inc. and co-founder of XBiotech and Urigen Holdings Inc. Mr. Bacha has been recognized as a *Top 40 Under 40* executive by Business in Vancouver magazine and is active in the community through volunteerism with the Leukemia & Lymphoma Society's Team in Training program and as chairman of the Board for Covenant House Vancouver, an organization dedicated to assisting at-risk and homeless youth to re-enter society. He earned his MBA from the Goizueta Business School at Emory University and his BSc in biophysics/pre-med from the University of California, San Diego.

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The 5 Whys

By: John A. Bermingham

One of the key business success factors that I have followed throughout the years is that of always trying to determine the root cause of any problem. The issue is that most people only look as far as the symptoms that are causing the problem and not the root cause, and there is an easy way to determine these causes, and it is called The 5 Whys.

Many moons ago, the founder of Toyota Corporation, Sakichi Toyota, developed a technique that was and is used within the corporation's manufacturing methodologies. It is still considered a critical component of problem-solving at Toyota today. The process is simply asking the question why five times. Let me provide you an example of only getting to the symptom of a problem.

-My car won't start (the problem)

Why?

-The battery is dead (the symptom)

So the solution to the problem is to recharge the battery. But the following week, you have the same dead battery problem. So you buy a new battery because it apparently will not take a charge. However, the following week, you have the same dead battery problem. Now let's take the same problem and apply The 5 Whys process.

-My car won't start (the problem)

Why?

The battery is dead

Why?

The alternator doesn't work

Why?

The alternator belt broke

Why?

It was worn, and I didn't replace it

Why?

I was too lazy

So the root cause as to why the car won't start is the person's laziness, not the dead battery. The dead battery is a symptom. The key is to urge the troubleshooter not to assume anything and to avoid logic traps. Instead, the solution is to follow the symptoms through The 5 Whys until you find the root cause of the problem.

Oftentimes, you will see that the root cause of a problem is because you have a flawed process in place or no process at all. In this case, you should be asking the question "what is the process that is in place, if there is one, and if so, is it the right process?" In addition, a key phrase to keep in mind in any five why exercise is "people do not always fail, sometimes processes do!" ◆

Biography

John A. Bermingham
Chief Operating Officer
1st Light Energy & Conservation Lighting

John A. Bermingham is currently the COO of 1st Light Energy & Conservation Lighting. He was previously Co-President and COO of AgraTech, a biotech enterprise focused on chitosan, a biomaterial processed from crustacean shells (shrimp, crawfish, crab, etc), as well as President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. Prior to Cord Crafts, he was President & CEO of Alco Consumer Products, Inc., an importer of house ware, home goods, pet, and safety products under the Alco brand name and through licenses from the ASPCA and Red Cross. He successfully turned around the company in 60 days and sold Alco to a strategic buyer. Mr. Bermingham was previously the President & CEO of Lang Holdings, Inc. (an innovative leader in the social sentiment and home décor industries) and President, Chairman, and CEO of Ampad (a leading manufacturer and distributor of office products). 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. He turned 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. Mr. Bermingham served 3 years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.

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