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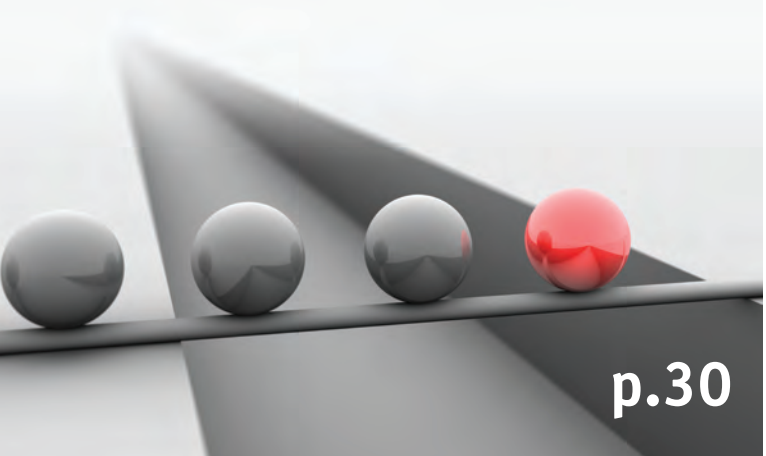
Bridging the Bioenhancement Gap

"Using its EmulSol technology, Ascendia has developed a novel oil-in-water nanoemulsion formulation of clopidogrel whereby the free-base form of clopidogrel has acceptable solubility in the oil phase, and is protected from chemical degradation. Ascendia continues to explore further development and partnering opportunities for this unique product."



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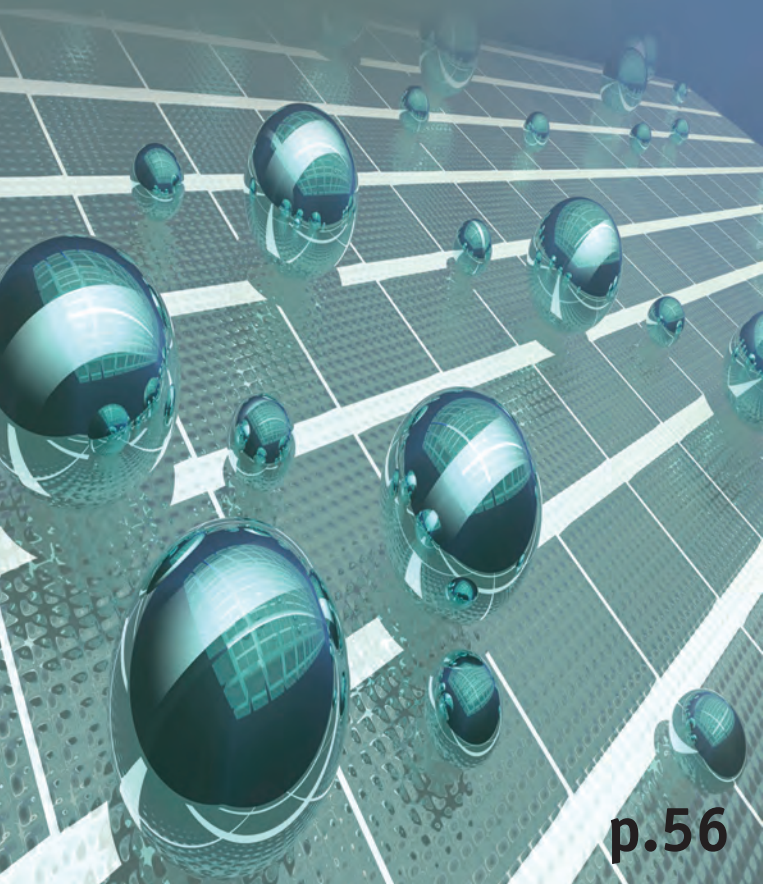
"Particle Sciences, Inc. (PSI) has developed a stable, hydrophobic nanoparticles technology that has the attributes of virus-like particles but with a much simpler architecture. They can be used to formulate vaccine antigens as particulates and link them to immunemodulators, such as TLR agonists at variable ratios and doses. This technology provides an efficient formulation platform for antigens and immunemodulators that can be optimized for both vaccine potency and safety profiles."



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Boehringer Ingelheim & CureVac Announce Major Development Collaboration

Boehringer Ingelheim and CureVac recently announced an exclusive global license and development collaboration. The new collaboration focuses on CureVac's CV9202, a novel investigational therapeutic mRNA vaccine in early clinical development for the treatment of lung cancer. Boehringer Ingelheim will start clinical investigation of CV9202 in at least two different lung cancer settings, in combination with afatinib in patients with advanced or metastatic epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer (NSCLC) and in combination with chemo-radiation therapy in patients with unresectable stage III NSCLC. CureVac receives EUR 35 million (approximately $45 million). Further, CureVac can achieve milestone payments of up to EUR 430 million (approximately $556 million) and royalties on sales.

This new agreement is part of Boehringer Ingelheim's long-term commitment to delivering tomorrow's cancer therapies through the discovery of novel treatment options with high therapeutic value for patients. The company's oncology portfolio includes afatinib, a once-daily kinase inhibitor that irreversibly binds and inhibits ErbB1, ErbB2, and ErbB4 receptors and is approved in a number of markets, including the EU and US. In the US, afatinib is marketed as Gilotrif for the first-line treatment of common types of EGFR-mutation positive metastatic NSCLC (Del 19 or L858R). Boehringer Ingelheim's oncology pipeline covers a broad range of solid tumors and hematologic malignancies (blood cancer), including two investigational compounds in Phase III clinical development: nintedanib in NSCLC and colorectal cancer, and volasertib in acute myeloid leukemia. These compounds are not approved and their safety and efficacy have not been established.

CureVac's mRNA-based technology represents a potential novel approach in cancer treatment. For the first time, mRNA could be optimized to mobilize the patient's own immune system to fight the tumor with a specific immune response elicited through the RNActive vaccine. Cancer immunotherapy has been chosen as the "Breakthrough of the year 2013" by SCIENCE magazine. CV9202 is a combination of mRNA molecules coding for six antigens overexpressed in lung cancer, designed to induce an immune response against the tumor. CV9202 and the preceding RNActive cancer vaccine CV9201 tested in initial clinical trials by CureVac demonstrated activity in generating immune responses against all anti-tumor antigens.

CureVac, a clinical-stage biopharmaceutical company from Tübingen, Germany, is pioneering the field of mRNA-based technology platforms for medical purposes with which mRNA is specifically optimized and formulated. Since 2000, the company develops novel mRNA-based cancer immunotherapies and prophylactic vaccines against infectious diseases – both under the brand RNActive. CureVac has successfully established the first GMP (good manufacturing practice) facility worldwide for the manufacture of RNA and mRNA and has pioneered mRNA-based drugs in clinical studies.

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And although we have a fresh new look and an equally bright perspective on the future, there's one more thing that hasn't changed. We're still the same people delivering the same great quality experiences for our clients. So get to know Metrics all over again.

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Foster Delivery Science to Build New Facility; Supports Increased Demand

Foster Delivery Science has recently broken ground on a new facility to support increased demand for manufacturing drug delivery and implant polymer blends. The facility is expected to be completed by May 1, 2015, at which time, it will be registered with the Food and Drug Administration (FDA) to allow for processing APIs.

Foster's new 32,000-sq-ft facility will be dedicated to HME processing of highly regulated materials and operate according to the cGMP regulations designated by the FDA. These materials are used for improving bioavailability and release rates of oral dose pharmaceuticals, as well as local delivery of APIs in implantable devices. Foster will offer custom drug/polymer blends in powder form for tablet pressing, or extruded into rods, film, or fiber for a wide range of drug delivery applications.

The new facility will include a 1,200-sq-ft ISO Class 7 clean room for processing materials and a 3,500-sq-ft cGMP warehouse for storage of APIs, raw materials, intermediates, and finished products. A comprehensive quality control lab will provide in-house material characterization, including microscopy, thermal analysis, spectroscopy, chromatography, and non-sink dissolution testing.

"We are one of the few companies dedicated to HME processing of APIs. Our success in formulation development, process development, and manufacturing of custom drug/polymer blends has exceeded our expectations and currently available space," said Tony Listro, Managing Director of Foster Delivery Science. "The new facility will allow us to increase our services in manufacturing of clinical supplies and larger production volumes."

Foster Delivery Science specializes in hot melt extrusion of drugs and polymer for pharmaceutical and combination drug-device applications. Foster Delivery Science is a wholly owned business unit of Foster Corporation, a leader in custom biomedical polymers for minimally invasive devices, implants, combination products, and pharmaceutical drug delivery.

Relmada Therapeutics Enters Agreement With Memorial Sloan Kettering

Relmada Therapeutics, Inc., a clinical-stage company developing novel therapies for the treatment of chronic pain, recently announced it has entered into an agreement with Memorial Sloan Kettering Cancer Center (MSKCC) in a series of animal studies for levorphanol, the active ingredient of LevoCap ER, a new tamper-resistant, extended-release form of levorphanol. Gavril Pasternak, MD, PhD, of MSKCC, is the lead investigator for these studies.

Dr. Pasternak said, "Levorphanol is a unique opioid analgesic that has been used clinically for decades. The purpose of these studies is to further characterize the actions of the drug at the molecular and behavioral levels based upon the current understanding of opioid mechanisms. The basic question is whether the actions of levorphanol can be dissociated from those of morphine and the more traditional opioid analgesics and whether these actions involve a novel subset of mu opioid receptor splice variants."

Eliseo Salinas, MD, MSc, President and Chief Scientific Officer of Relmada Therapeutics Inc., added, "Unlike oxycodone, morphine, hydromorphone, oxymorphone, and hydrocodone, levorphanol seems to modulate pain through mechanisms common with those traditional opioids (the ascending opioid pathways) as well as a unique combination of mechanisms involving delta, kappa, and N-methyl-D-aspartate (NMDA) receptors, the norepinephrine and serotonin transporters, as well as different variant of the mu opioid receptor described by Dr. Pasternak's group. This unique combination of mechanisms may explain its efficacy and its ability to partially reverse tolerance to morphine."

Sergio Traversa, CEO of Relmada Therapeutics, concluded, "Relmada is delighted to work with Dr. Pasternak and his team at Memorial Sloan Kettering. MSKCC has done amazing, pioneering work on pain mechanisms, and their experience with levorphanol is ideal for our research. Our company is dedicated to finding new ways to treat and manage pain, and the methodologies of this kind of research have evolved since levorphanol was last examined in detail a couple of decades ago. We are confident that new treatments for pain are needed, and we believe that levorphanol's promise is worth the greatest consideration. In addition, Relmada remains dedicated to further research and development into d-methadone, the NMDA receptor antagonist for neuropathic pain; BuTab ER, an oral dosage form of the opioid analgesic buprenorphine; and MepiGel, a FDA Orphan Drug designated topical formulation of the local anesthetic mepivacaine."

Relmada Therapeutics is a clinical-stage, public specialty pharmaceutical company, focused on developing novel versions of proven drug products together with new chemical entities that potentially address areas of high unmet medical need in the treatment of pain.

TapImmune Releases Positive Interim Data for Ovarian & Breast Cancer

TapImmune Inc. is extremely pleased to report that analysis of the interim data from the first 13 patients in a Phase I clinical trial show that each of the patients treated have raised specific T-cell immune responses against a set of five naturally processed folate receptor alpha Class II antigenic epitopes. All five of the constituent peptides were found to be immunogenic and all patients developed immune responses to at least one and in most cases more than one of the vaccine peptides.

The trial is fully accrued and as of August 26, 2014, all 22 patients had completed their vaccinations. Eight women with HER2-negative breast cancer, 13 with ovarian cancer and one with fallopian tube cancer were enrolled.

Glynn Wilson, TapImmune's CEO, stated "In general, the vaccine has been well tolerated. This is the first positive endpoint we have reported for the clinical study on folate receptor alpha antigens and when taken together, the promising data on safety and immune responses are tremendously encouraging and provide a clear scientific rationale for progressing to a Phase II Clinical Trial In addition to the primary Ovarian indication, this set of antigens and our approach fills a significant need for treatments for difficult to treat cancers for which targeted therapies are not available, for example Triple-negative breast cancer."

The Phase I trial is being carried out at the Mayo Clinic, Rochester, MN. TapImmune has an Exclusive Option to License this antigen technology.

TapImmune Inc. is an immunotherapy company specializing in the development of innovative vaccine technologies for the treatment of cancer and infectious disease. The company's vaccine compositions, peptide or nucleic acid-based, comprise one or multiple naturally processed epitopes (NPEs) designed to comprehensively stimulate a patient's killer T-cells and helper T-cells and to restore or further augment antigen presentation by the modulation of TAP (Transporter associated with Antigen Processing). The company believes that its vaccine compositions may be used as stand-alone medications or in combination with current treatment modalities.

Seattle Genetics & Genmab Enter New ADC Collaboration

Seattle Genetics, Inc. and Genmab A/S recently announced the companies have entered into an additional antibody-drug conjugate (ADC) collaboration. Under the new agreement, Genmab will pay an upfront fee of $11 million for exclusive rights to utilize Seattle Genetics' auristatin-based ADC technology with Genmab's HuMax-AXL, an antibody-targeting AXL that is expressed on multiple types of solid cancers. Seattle Genetics is also entitled to receive more than $200 million in potential milestone payments and mid-to-high single-digit royalties on worldwide net sales of any resulting products. In addition, prior to Genmab's initiation of a Phase III study for any resulting products, Seattle Genetics has the right to exercise an option to increase the royalties to double digits in exchange for a reduction of the milestone payments owed by Genmab. Irrespective of any exercise of option, Genmab remains in full control of development and commercialization.

"This collaboration with Genmab further extends the reach of our industry-leading ADC technology for use with novel oncology targets, while providing us with a compelling financial value proposition as the program advances," said Natasha Hernday, Vice President, Corporate Development at Seattle Genetics. "Genmab's impressive track record in the development of antibody-based therapies for the treatment of cancer, including an ADC in a Phase I clinical trial for solid tumors utilizing Seattle Genetics technology from our first agreement, make them a strong partner for this new collaboration."

"This new collaboration with Seattle Genetics adds another ADC program to our innovative preclinical pipeline of antibodies developed using the latest technological advances in cancer therapeutics. Preclinical work identified AXL as an excellent target for an ADC therapeutic approach," said Jan van de Winkel, PhD, Chief Executive Officer of Genmab. "Accessing state-of-the art technology of companies such as Seattle Genetics who are experts in their field provides another means for Genmab to develop differentiated cancer therapeutics while retaining maximal ownership of our therapeutic products."

Seattle Genetics and Genmab entered into an ADC collaboration for HuMax-TF-ADC in September 2010. HuMax-TF-ADC, targeting the Tissue Factor antigen, is in a Phase I trial for solid tumors. Seattle Genetics has the right to exercise a co-development option to share all future costs and profits for HuMax-TF-ADC at the end of Phase I.

HuMax-AXL-ADC is an ADC combining a high affinity human monoclonal antibody against AXL with Seattle Genetics' clinically validated cytotoxic drug. AXL is a signaling molecule involved in multiple processes of tumor development and progression. The target molecule is highly expressed on a variety of solid cancers.

Edge Therapeutics Gets $10 Million From Hercules Technology

Edge Therapeutics recently announced it has obtained up to $10 million in venture debt financing from Hercules Technology Growth Capital, Inc. (HTGC), to support the continued development of EG-1962, the company's lead product candidate.

"We are very pleased to enter into this loan agreement with Hercules, one of the leading specialty finance companies in the life sciences sector," said Brian Leuthner, Chief Executive Officer and President. "With the additional access to capital, we remain on our path to delivering top-line data from the ongoing NEWTON trial for EG-1962 by the first half of 2015 while limiting shareholder dilution."

Edge is developing EG-1962 to fundamentally improve patient outcomes and transform the management of aneurysmal subarachnoid hemorrhage. The company believes that EG-1962 can become the new standard of care for patients suffering from a ruptured brain aneurysm who receive an intraventricular catheter.

The $10 million ($3 million of which was drawn down at closing, and the balance of which is available upon the satisfaction of certain milestones) in funding from Hercules is in the form of secured indebtedness.Payments under the loan agreement are interest only for 12 months, followed by 30 equal monthly payments of principal and interest through the scheduled maturity date on March 1, 2018.

EG-1962 is a novel polymeric nimodipine microparticle that is administered directly into the brain ventricles. A single dose of EG-1962, administered initially at the time of aneurysm repair, delivers a high concentration of nimodipine directly to the brain, with sustained drug exposure over 21 days. EG-1962 utilizes Edge's proprietary, programmable, biodegradable polymer-based development platform, known as Precisa. The Precisa platform allows Edge to create therapeutics capable of delivering medicines directly to the site of injury, providing a novel delivery mechanism that enables targeted and sustained drug exposure while potentially avoiding the systemic, dose-limiting side effects often associated with current standards of care. EG-1962 is currently being evaluated in the Phase I/II NEWTON study, a safety, tolerability, and pharmacokinetics clinical trial.

Ascendia Advances, Successfully Applies Nano-Emulsion Technology Platform

Ascendia Pharmaceuticals, a start-up specialty pharmaceutical company in the business of providing formulation technologies and product development services for poorly soluble molecules, recently announced the company has successfully applied its nano-emulsion technology platform to a novel injectable formulation of clopidogrel - the world's top-selling blood thinner medicine. Ascendia has advanced the program to pre-IND development stage, and has filed US and worldwide PCT patent applications on the product.

"There is a significant unmet medical need for a parenteral clopidogrel dosage form for the treatment of Acute Coronary Syndrome under life-threatening situations," said Jingjun "Jim" Huang, PhD, CEO of Ascendia. "With our nano-emulsion platform technology, Ascendia has demonstrated that a ready-to-use, stable and soluble, parenteral form of clopidogrel is both technically and commercially feasible - by addressing the solubility, physical, and chemical stability, API sourcing, manufacturing, and delivery challenges of this difficult compound."

ASD-002 is a parenteral form of clopidogrel formulated as an oil-in-water nano-emulsion suspension. Ascendia is developing ASD-002 for the treatment of Acute Coronary Syndrome - which refers to either unstable angina or when blood supply to the coronary arteries becomes suddenly fully or partially blocked (ie, a myocardial infarction). When a patient presents with a suspected coronary event, a 300- to 600-mg loading dose of clopidogrel is frequently administered. However, the only commercially available dosage forms of clopidogrel are oral tablets in 300- and 75-mg strengths - not ideal for administration in an emergency setting. Also, when delivered orally, there is a significant delay in the time required for the medicine to become effective - although clopidogrel is rapidly absorbed, the time to reach peak concentration and therapeutic effect can require several hours. Therefore, in an acute, emergency setting, a more rapidly acting, injectable clopidogrel dosage form is desirable.

The barrier to developing such a product is due to clopidogrel's challenging solubility, physical form, and chemical stability properties. Clopidogrel is practically insoluble in water (the oral tablet composition uses the bisulfate salt form of clopidogrel, which is soluble at gastric pH, but not suitable for injection). Clopidogrel free-base is a semisolid, viscous, oily form, thus presenting difficulties in storage, dispensing, and processing. Moreover, the free-base form is chemically unstable and undergoes both hydrolysis and oxidation. In addition, clopidogrel is a chiral molecule - only the Senantiomer is biologically active, and chiral conversion to the R-enantiomer can easily occur in a liquid dosage form. ASD-002 overcomes these stability and delivery challenges by stabilizing the free-base form of clopidogrel in the nano-emulsion formulation.

Catalent Supports Lilly's Clinical Trials Needs, Makes Major Invetsment

Catalent recently announced that it is to install new automated prefilled syringe clinical packaging lines at its Philadelphia Clinical Supply Center of Excellence, in support of the growth of its strategic partner, Eli Lilly.

Catalent already has automated prefilled syringe packaging capabilities in its clinical supply facility in Schorndorf, Germany, providing end-to-end clinical supply solutions from clinical supply management, comparator sourcing and primary packaging to storage and distribution globally.

The packaging line is capable of the fully automated insertion of plunger rods, application of randomized and non-randomized labels and back-stop clips, and off-line labeling with booklet labels. This investment reflects a strong commitment from both Catalent and Eli Lilly to continue shared growth strategies, risks, and to build a long term strategic partnership.

"Our continued investments in clinical packaging, cold chain storage, digital solutions, and our expansion into China are all part of our growth strategy and commitment to our customers to help them reduce clinical trial timelines," commented Gerry Hepburn, Chief Operating Officer, Vice President and General Manager of Catalent's Clinical Supply Services business. "Our strategic partnership with Eli Lilly supports their innovation by bringing more products faster to market."

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

DPT Laboratories Acquires Meda Pharmaceuticals' New Jersey Location

DPT Laboratories, a contract development and manufacturing organization (CDMO) with a specialized focus on semi-solid and liquid dosage forms, recently announced the acquisition of Meda Pharmaceuticals' Lakewood, NJ, facilities.

The acquisition reflects the organization's recent growth, allowing DPT to expand its footprint in Lakewood by adding two buildings totaling 90,000 square feet of space. The real estate meets the organization's current need for additional cold storage and a larger state-of-the-art analytical laboratory.

"The Meda Pharmaceuticals space allows us to meet the needs of our clients today and beyond," said Gene Ciolfi, Vice President and General Manager, Lakewood site operations. "We are also in a better position to explore additional opportunities to further our capabilities from development through commercialization."

As part of the acquisition, DPT will also absorb Meda Pharmaceuticals' employees to continue the manufacturing of MUSE, its urethral suppository product.

"We look forward to transitioning Meda Pharmaceuticals' personnel to the DPT team," Ciolfi commented. "Their experience and continued dedication to quality complements our commitment to outstanding client service."

DPT's current Lakewood location is one of the organization's established Centers of Excellence. This center provides state-of-the-art aseptic processing suites and filling equipment for small-volume parenterals, ophthalmic preparations, preservative-free nasal sprays, and sterile ointments.

DPT is a CDMO helping pharmaceutical companies achieve clinical and commercial success. With five cGMP-compliant facilities in San Antonio, TX, and Lakewood, NJ, DPT applies a Quality-by-Design (QbD) methodology to investigate its clients' products, and discover and deliver the optimal solutions from development through commercialization.


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Management Insight

CDMOs Take Flight: Business Lessons From the Airline Industry

By: Derek Hennecke, CEO & President, Xcelience LLC

I'm writing this article in an airplane. I spend a lot of time up here, and there's a good chance you do too. Let's take a moment, then, to reflect on the similarities between the airline business and our own. In my opinion, there is no industry more similar to ours.

It may not seem so on the surface. Most of the planes you fly on cost between $200 and $300 million; an Xcelodose costs $500,000. Most passengers switch airlines constantly based on schedules and routes; a CDMO partners with a client for months or years at a time. And yet, when you scratch a little deeper, our industry flight paths are not so different.

LACK OF CAPACITY LOSES CUSTOMERS

Like the airline industry, CDMOs suffer from capacity issues. The airline wants to fill every seat, every day. The CDMO wants to run every machine, all day. But neither industry will ever achieve that ideal, because it means turning away customers when capacity is reached. In our industry, more than in the airline industry, a client scorned due to lack of capacity is a client lost. The airlines have compromised with a load factor of about 60%, at which point 7% of flights are full and unavailable. A load factor of 70% would result in 21% being turned away.

Our industry lacks statistics regarding load capacity, and even if such figures existed, they would vary widely based on the equipment and service involved. At Xcelience, we find that in most cases, we can maintain a load around 70% without having to turn any customers away. The challenge is in anticipating increasing demand because of the long lead times required to increase capacity.

UNUSED CAPACITY EXPIRES

Once a plane takes off, all empty seats are lost potential revenue. The incentive, then, is to fill those seats for any dollar amount. The CDMO industry is no different. An idle machine or lab technician is a lost earnings opportunity. This differs from, for example, the manufacturing industry. A shoe factory can stockpile shoes for a while and slowly adjust capacity to meet demand over time.

Airlines and CDMOs cannot shed capacity with ease. The market for used planes is weak, as is the market for tablet presses and roller compactors during a recession. However, airlines can add capacity more quickly than CDMOs. Planes can be leased. For CDMOs, leasing is less common and, even when possible, time-consuming training and installation procedures must follow.

DEMAND FLUCTUATES

For the most part, neither industry can influence demand. The result is that both industries are sometimes buffeted by the economic winds around them, and must adjust course.

FIXED COSTS ARE HIGH

Because airplanes and terminals don't come cheap, airlines are incentivized to fly their aircraft as much as possible, even if incremental flying doesn't produce enough revenue to cover all costs. Routes are optimized to minimize non-full flights, but if a flight is unexpectedly under-booked, it's better to book as many passengers as possible at any price, if only to cover the variable costs like fuel and peanuts. CDMOs are no different, economically. We are incentivized to use our equipment rather than let it sit idle, even if it's booked at a rate that doesn't cover our depreciation and other fixed costs. We don't offer peanuts, so we have almost no variable costs at all. But whereas the airlines have no reason not to sell that last seat whatever the cost, in our industry, this isn't completely so. The closer we are to full capacity, the less flexibility we have to meet our existing customers' sometimes unpredictable needs.

ADDING NEW SERVICES CREATES GEOMETRIC EFFECTS

When an airline adds a new hub, it is, in effect, increasing production. In most industries, increasing production doesn't really improve your competitive offering, but in the airline and CDMO industries, it does. When an airline adds a new city, it doesn't just give customers one more buying opportunity, it gives customers access to a new hub with all the flights offered out of that new terminal. A 50% increase in the number of cities added to a network (say 9 to 14) more than doubles the number of city pairs from 45 to 105. Similarly, adding an XPRD makes it more likely at Xcelience that we will sell DSC and TGA work. Having a bi-layer press brings more work for analytical. The effects are geometric, rather than additive.

Here's an important difference

though; when an airline adds a new city, service to that city is the same as service to any other city. When a CDMO adds, for example, toxicology, there is a whole skill set associated with the new capability. The CDMO must take care to offer this new skill set at the same high level as its other capabilities (for the sake of reputation), and must maintain enough business to keep those people busy enough to justify their salaries and to keep their skills honed.

Of course, not all additions will have the desired geometric affect. The capacity added must be the right fit for the CDMOs offerings, and for the times. It's fashionable right now, for example, to add preformulation to API or drug product suppliers. We did this at Xcelience several years back, and our X-Ray Diffraction and accompanying polymorph screening work is solidly busy. But when we added this capacity, we were filling a vacuum created when Aptuit bought SSCI back in 2008, and Steve Burns and his team subsequently left SSCI. Things are different now. Just because a company can afford the equipment doesn't mean it will have the expertise or the work to keep a core group of scientists busy enough for their tools to remain sharp. You can't dip your toes in the same river twice.

Pursuit of the geometric growth effect is what drives the trend toward one-stop shops in the CDMO world. In the current market, this effect is muted by the fact that demand is outstripping supply, but if history proves correct, as the market slows, oversupply will increase. This too mirrors the airline industry, where the saying goes that all new planes are ordered in good times and delivered in the bad.

REPUTATION MATTERS

Word of mouth remains a powerful thing in both industries, and even more so for CDMOs. With airlines, people choose primarily based on schedule and price. Frequent flyer points and lounges can stimulate some loyalty, but ultimately, a plane is a plane, and you are only in it for a few hours. It doesn't matter too much which airline you take, and you can change your mind next time if you aren't happy this time. A CDMO is a longer-term partnership with higher switching costs. Most importantly, a manager who chooses a CDMO is to some extent putting his/her own career at risk. If the CDMO disappoints, time and API have been lost, and switching requires research, visits, contract negotiations, relationship building, and some re-learning (not all CDMOs operate alike). Reputation trumps price in CDMO selection.

EMPLOYEES ARE THE FACE OF THE COMPANY

You may well argue that safety is job one in the airline industry, and quality in ours. Really, though, both of these are givens as industry regulations make them a barrier to entry. The next most important thing to clients/passengers is the people you deal with. At Xcelience - after technical knowledge - the most important employee attribute we look for is attitude. I believe most of us would agree that the airlines are lousy at this, with one exception, and that is Southwest. Southwest Airlines used to give job candidates a funny photo of the CEO. If the potential hire didn't laugh, he or she didn't get an offer.

MARKETS FAVOR CONSERVATIVE GROWTH

Both industries resist growing too quickly. Braniff Airlines once famously added 32 new routes and 16 cities in a 24-hour period. The company added every possible aircraft to the line, including the Concorde. Costs skyrocketed, and it became apparent that there was a reason no other airline had ever offered a direct flight from Buffalo to Orlando. Quality suffered as the company struggled to absorb so many changes at once. It took more than 24 hours to achieve bankruptcy, but the company's descent from the skies was stomach-dropping just the same. Southwest Airlines, by contrast, took 12 years to go from two aircraft to 50.

In the CDMO world, substitute the name of Braniff for Azopharma. Many of us witnessed the famous 2008 AAPS, where 80 new sales reps, fresh from careers selling shoes or cars, cordoned the outside of their booth on freshly combed carpet. Azopharma came out of nowhere in mid-2005, and was gone by Good Friday of 2009.

ARE WE MISSING THE PLANE?

Any talk of similarities must inevitably lead to talk of unrealized opportunities. What are the airlines doing that we aren't?

1. Increasing Demand

I mentioned already that demand in both industries is outside of the industries' control. Or is it? Southwest proved that the airline passenger pie is not as fixed as everyone said it was. The airline created short, cheap commuter flights that competed for the travel dollars of car drivers, train, and bus passengers. In our industry, price is not going to increase demand the same way. The only way to increase the pie is to encourage large pharma to outsource more development. One way to do this is to co-invest in large pharma customer's products. Another possibility is to go into a consortium. In this case, the consortium would consist of a group of CDMOs buying a drug or drugs from large pharma in Phase I, bringing them into Phase III, and then selling them back to large pharma.

2. Add-On Fees

Xcelience has consciously chosen not to use add-on fees, but some people in our industry believe they will inevitably come. The airlines have blazed through the learning curve on add-on fees, and any company considering them would do well to heed their mistakes. Studies have shown that customers feel less betrayed when asked to pay for something they consider a luxury, such as Wi-Fi or entertainment. Being charged for something that used to be free brings much higher levels of resentment, though there are nuances. Paying for legroom that was once standard had a dramatic effect on consumer frustration, as did requiring them to pay for carry-on baggage. But being hit with an extra fee for an oversize bag was not so bad. How would a client feel if hit with a bill for QA work done at the CDMO? Not good, undoubtedly. All of these scenarios involve greater or lesser degrees of negative impact, and thus are not a road to be embarked on without trepidation. Still, from a business perspective, airline add-on fees have been irrefutably successful, earning the industry $5.6 billion in 2011.

3. Stock Ownerships, Annuity Investments & Profit-Sharing Plans

The only long-term, profitable airline at the moment is Southwest, a fact attributed among other things to CEO Herb Kelleher's outstanding job of integrating labor and management to build a creative and happy workforce. Not the least among his efforts is Southwest's employee stock ownership, annuity investments, and profit-sharing plans. While such plans do put employee earnings at risk, they generally offer greater rewards over time, and they impart a sense of ownership that brings employee/management interests together. Xcelience is the only CDMO I'm aware of that moved to an aggressive quarterly bonus pool based on profits and revenue goals. When we did this 3 years ago, we didn't reduce base salaries. The bonuses were added as a new incentive. Still, the move met with resistance at first. While everyone appreciated the new earnings opportunity, some asked if it could be implemented as a straight, guaranteed salary increase instead. Shared ownership of the company's success is a culture change, to be sure. Our employees are used to it now. The company and the employees' interests are more aligned than ever, and this lesson from the airline industry is definitely an engine that is fueling our growth. ◆

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BIOGRAPHY

Derek G. Hennecke is President and CEO of Xcelience, a CDMO in formulation development and clinical packaging located in Tampa, FL. Mr Hennecke launched Xcelience as a management buyout in 2006, and the company has more than tripled in size. Prior to starting Xcelience, Mr. Hennecke worked for DSM as a turn-around manager in the global drug development community, managing an anti-infectives plant in Egypt, technical and commercial operations in a JV in Mexico, and a biologics facility in Montreal. He developed the formulation and business strategy of several drug compound introductions such as clavulanic acid, erythromycin derivatives and Tiamulin. A Canadian, he covets the Florida sun, but can't be kept away from the rink for long. He is an avid fan of the Tampa Bay Lightning.

Getting It Right: The Importance of End-User Research in the Design of a New Drug Delivery System

By: **Chris Evans**

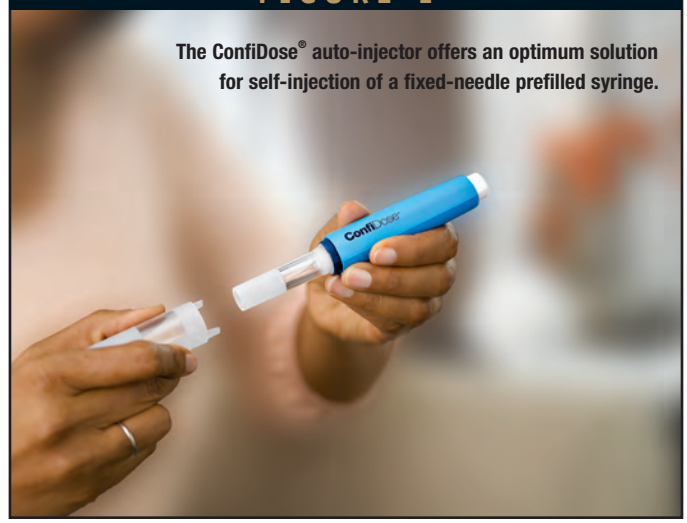
To design a drug delivery system that will truly resonate with patients, one must first understand the behaviors and motivations of the intended user groups. This requires insight into the unique experiences of those users by conducting research that will drive innovation in the design and development process to create a solution that works in a variety of situations.

Drug manufacturers agree that end-user research and human factors testing are critical when considering the design of a new drug delivery system, such as self-injection devices for diabetes patients. Historically, many companies have relied on patient focus groups to obtain information about user considerations for drug administration systems. However, focus groups don't always offer the full picture on how patients use drug delivery devices at home, work, and other settings. Initiated partially by evolving regulatory requirements, pharmaceutical manufacturers have begun taking a more personalized approach to understanding end-user needs in various environments and ultimately developing products that can better help patients adhere to treatment regimens.

A common sense approach lies at the core of human factors engineering. In order to mitigate the risk associated with user error or misunderstanding, design options must be considered in the context of how a human interacts with the device and the world surrounding him or her at the time of use.

For the pharmaceutical delivery device industry, understanding how the human factors world defines and evaluates human capabilities is a large part of the puzzle. Design experts must try to understand the human condition of the user, an important consideration throughout the design process. Working with human factors and user-research professionals, designers can learn more about how an evolving disease state can affect device use in self-therapy situations. They then can help reduce user-based error, and control or reduce current and future risks associated with device use by employing a flexible set of design tools that will help refine and enhance the delivery devices or interfaces. Such refinements can help to create a system that not only aids in the effective delivery of a drug product, but enhances the user experience and potentially gains brand loyalty for the pharmaceutical manufacturer during the entire course of treatment.

FIGURE 1



The ConfiDose® auto-injector offers an optimum solution for self-injection of a fixed-needle prefilled syringe.

DESIGNING FOR THE HUMAN CONDITION

Human factors engineering and usability testing seeks to gain a thorough understanding of the potential users' behaviors, motivations, and needs. Three main components for device testing will help optimize how people interact with technology: 1) device users, 2) device use environments, and 3) device user interfaces. Using in-depth statistical analysis, data aggregation and synthesis techniques should yield actionable opportunities for innovations and enhancements that will help make the delivery systems easy to use throughout the treatment regimen. For those with chronic conditions, the proper delivery system will help meet emotional and physical needs not only when first diagnosed, but also as they become comfortable with long-term care options.

Human factors experts should start by determining what must be known about the user and the device interaction before selecting one of the many research tools available. Methods include:

Qualitative: interviews, ethnographic observation, contextual inquiry, and concept evaluation

Quantitative: questionnaires, in-person surveys, and user-based performance testing

Analysis & Synthesis Outputs: affinity diagramming, product adoption road maps, and habits and ideal scenarios

Human Factors/Ergonomics: human error and risk analysis, usability testing, and heuristic analysis (encouraging a person to use the device on his/her own)

A strong framework for the development process can be gained through the use of discovery research, directional and preference testing, and usability testing. Customers' needs and desires can be confirmed through discovery. Directional research allows users to evaluate product concepts, and usability testing helps to ensure that the delivery solution is appropriate for users. Usability testing offers a more robust framework that can be broken down into four major components. They are:

FIGURE 2

The West SmartDose® electronic wearable injector, designed for patient convenience, uses a Daikyo Crystal Zenith® cartridge and can deliver a dose of up to 3.5 mL, which may allow for viscous biologics to be administered over longer periods of time.

Physical Abilities: anthropometry (the measure of bodies, such as heights or the size of hands), biomechanics (what can be accomplished physically), and sensory abilities (vision, hearing, tactile sense)

Cognitive Abilities: how people process information, the capabilities of memory, the manner in which humans learn new things, and how habits are developed

State of Being: the general health of the expected user, disease states and co-morbidities, mental and emotional states, and motivation for learning new things

Experiences: educational background, knowledge of a particular disease state, and lifelong experiences with objects that will guide behavioral interactions with any delivery system

These components help make important connections in

the relationship between the user and the device. Typically, the best data is gathered through interviews in the proper context. Seeing the user in the midst of daily distractions, such as caring for an aging parent and interacting with children, pets, ambient noise, temperature, and lighting, all help human factors experts better understand how the patient will use a device. Also, usability may change over time as the patient becomes more accustomed to a device.

Patient needs also must be defined appropriately. Three types of needs are important to the success of any development program. Different techniques can be used to elicit and discover these needs, which include:

Expected Needs: Needs that are meaningful to patients; direct observation inside the user's environment is an effective way to document these types of needs

Expressed Needs: Needs that are simple for users to articulate; "think-alouds" and other narrative techniques are best to determine expressed needs

Exciting Needs: This type of "need" typically delights patients because they often do not think about the possibilities as technically possible. Reaction to emotive stimuli, scenarios and storytelling are ways to elicit emotionally based needs

While there are many methods available to test usability and reduce user-based risk, understanding how the patient interacts with the user interface can help ensure optimal device design. The ability to operate a device successfully depends on several conditions including the patients' mental and emotional state, the environment in which they are using the device, and previous knowledge of and experience with similar devices. At West, taking all of these variables into account is critical to our design process. We employ human factors principles and conduct extensive usability testing during the device design phase that will not only meet the unique needs of our pharmaceutical partners, but more importantly, also ensure the device is safe, effective, and consistently delivers the intended treatment to patients. ◆

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BIOGRAPHY

Chris Evans is the Director of Innovation, Pharmaceutical Delivery Systems at West Pharmaceutical Services, where he manages teams for discovery/user research, human factors, and conceptual and intellectual property development. He has more than 20 years of experience in product development, with extensive expertise in healthcare packaging and device development. Mr. Evans earned his BS in Biology from the University of Maryland.

NANOEMULSION FORMULATIONS

Nanoemulsion Formulations for Injection & Oral Administration

By: Troy M. Harmon, MS, MBA, and Jingjun Huang, PhD

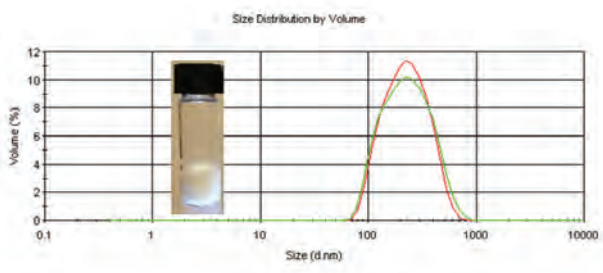
INTRODUCTION

Oil-in-water emulsions, which are composed of oil droplets dispersed in an aqueous continuous phase, can provide unique solutions for overcoming drug solubility and stability problems. In general, emulsions have many practical applications in the agriculture, food, cosmetic, pesticide, and pharmaceutical industries.[1] One of the uses of emulsions is to deliver active pharmaceutical ingredients (APIs) in topical, oral, nasal, ophthalmic, or injectable dosage forms. Although a number of lipid-based nanoemulsion pharmaceutical products have been marketed in the past 20 years, there are fewer examples of oil-in-water emulsion products. Examples include Diprivan® (propofol), an injectable anesthetic, and Restasis® (cyclosporin), an opthalmic drop for dry-eye syndrome.

Emulsions can be characterized as macro, micro, or nano. Macroemulsions are typically opaque in appearance, as the average particle size of the hydrophobic droplet in a macroemulsion is typically > 500 nm and thus scatters light. Microemulsions and nanoemulsions are obtained when the size of the droplet is typically in the range of 50 to 500 nm. In addition, emulsions in this size range can appear translucent or optically clear if the average oil droplet size is < 100 nm, as droplets in that size range no longer scatter light. Furthermore, emulsions with droplet sizes below 100 nm have the added benefit of aiding the drug to penetrate epithelial mucosol layers such as in the eye, skin, nasal, lung, GI tract, tumor, blood-vein, and blood-brain barriers.

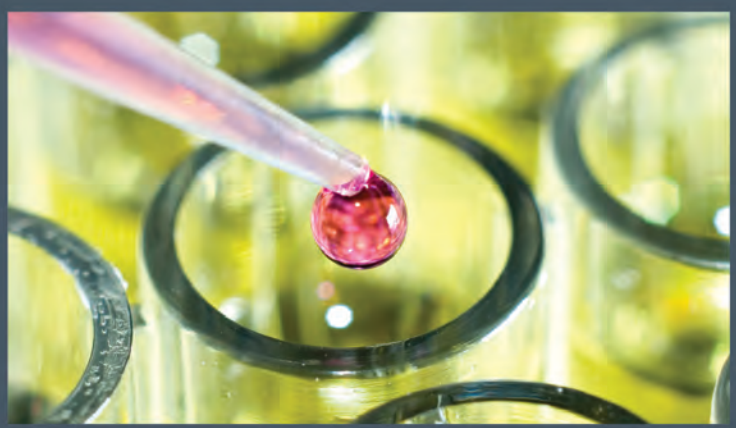
The distinction between microemulsions and nanoemulsions relates to their thermodynamic stability. Microemulsions are thermodynamically stable due to the use of sufficient co-solvents and co-surfactants to prevent Ostwald ripening - essentially the coalescence of the droplets into larger particles. Ostwald ripening is the most frequent instability mechanism, although gravitational separation can also occur with larger particles.[2] Nanoemulsions contain much less of the stabilizing co-solvents and co-surfactants, and as such are meta-stable and more susceptible to Ostwald ripening. In addition, nanoemulsions require greater kinetic formation energy, and are usually prepared using high-pressure homogenization or ultrasonic generators. Because of

FIGURE 1



Oil Droplet Particle Size of ASD-002 (Clopidogrel Nanoemulsion)

Excipients for Smart Drug Delivery Solutions



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the undesirable side-effects caused by many solvents and surfactants (in fact, the FDA places daily intake limits on such ingredients), microemulsions are disadvantageous compared to nanoemulsions. This is also true when using an emulsion process to develop a liquid pediatric dosage form as many surfactants have a bitter taste.

EMULSOL TECHNOLOGY

A drug's low solubility often presents a serious challenge to developing bioavailable dosage forms. This challenge can be exacerbated for drugs with chemical stability issues when solubility-enhancing approaches utilize excipients that are incompatible with the drug substance. To overcome these challenges, many technologies have been developed, including particle size reduction to nanometer-size drug crystals with greater surface area for dissolution, production of amorphous solid dispersions for reducing the energy required for dissolution, and lipid-based drug delivery systems for dissolving a hydrophilic drug in either a lipid or oil phase. However, not all of these technologies are suitable when the drug is both poorly soluble and chemically unstable. In particular, the use of nanoemulsions is a growing area due to their ability to formulate poorly soluble drugs for multiple routes of administration - drops or creams for topical products, suspensions for pediatric products, and sterile, parenteral forms for injection, and to potentially shield the active ingredient from chemical degradation.

TABLE 1

	Aqueous Concentration (mg/ml)	Comments
Clopidogrel Free-Base	7 mg/ml @ pH 1 buffer	Highly pH dependent solubility
	0.002 mg/ml @ pH 7.4 buffer (simulated plasma pH)	Solubility crashes at higher pH
ASD-002 Nanoemulsion	> 200 mg/ml in oil phase	Formulation suitable for 505(b)(2)
	> 20 mg/ml loading in total volume of nano-emulsion	300 mg dose can be delivered with a 10-15 ml injection

Solubility of Clopidogrel Free-Base & ASD-002 Formulation

EmulSol™ is Ascendia's proprietary technology for production of novel oil-in-water nanoemulsions. Despite their advantages, nanoemulsions have certain limitations. The oil droplet particle size may increase over time via Ostwald ripening - this physical instability can lead to loss of optical clarity and potentially a decrease in drug solubility as the interfacial surface area decreases. In order to achieve physically stable nanoemulsions, long-chain triglyceride oils are sometimes employed, but typically require the use of organic co-solvents or toxic co-surfactants (eg, Cremaphor). The addition of co-solvents and co-surfactants significantly reduces the safety and tolerability profile of the pharmaceutical formulation. These excipients may not be suitable for pediatric administration, may cause injection site pain and irritation, and are becoming less acceptable in general for use in pharmaceutical formulations.

Ascendia's EmulSol technology produces stable, optically clear nanoemulsions without the use of organic solvents and with minimal use of co-surfactants using a high-pressure homogenization process. By selecting specific long-chain triglycerides in combination with an ionizable surfactant, Ascendia has eliminated the use of organic solvents in its formulation approach. EmulSol formulations are prepared using a conventional homogenization process, but with a proprietary combination of oils and surfactants (patent pending) - the resulting suspension of oil droplets in the water

MORE TECHNOLOGY.

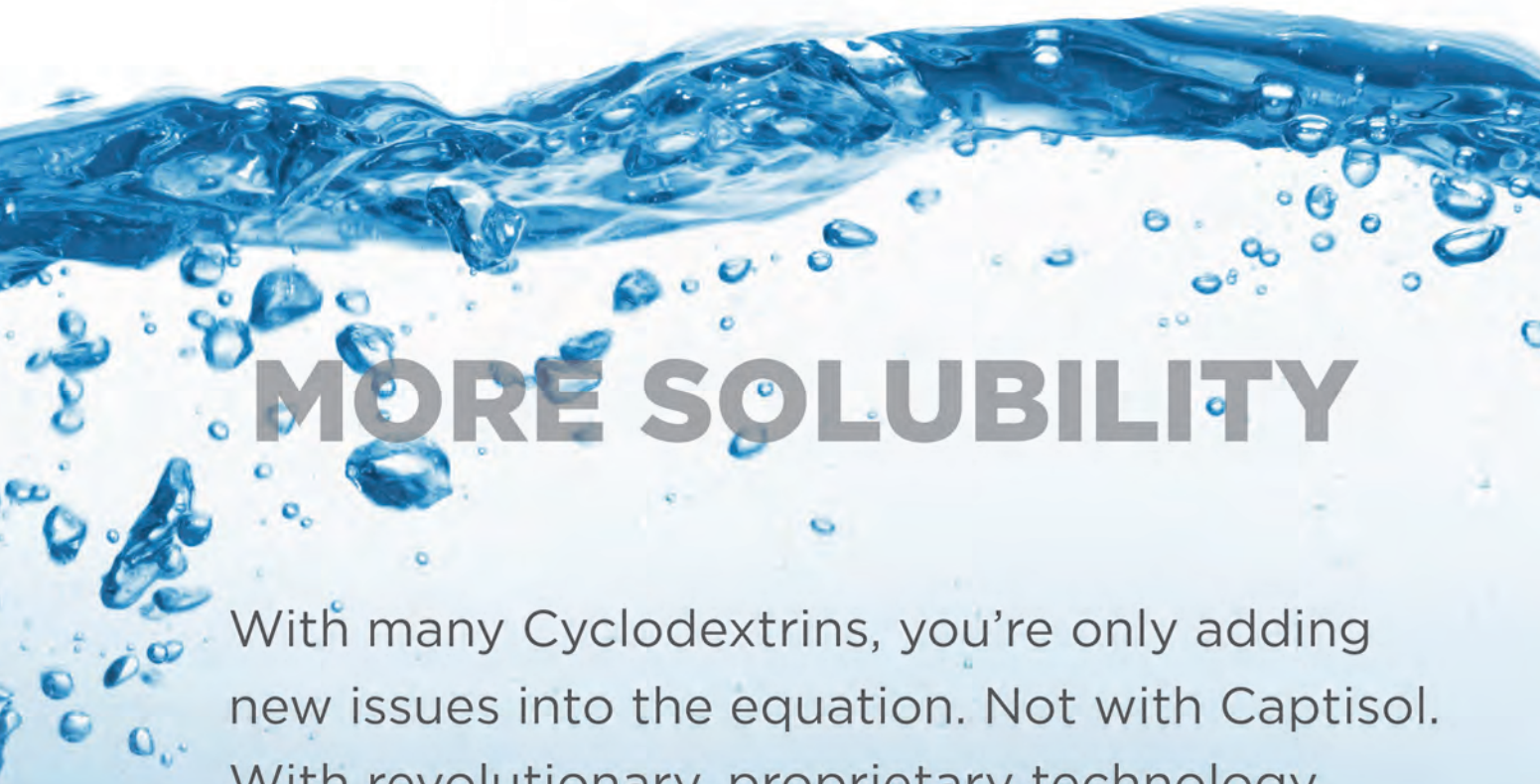

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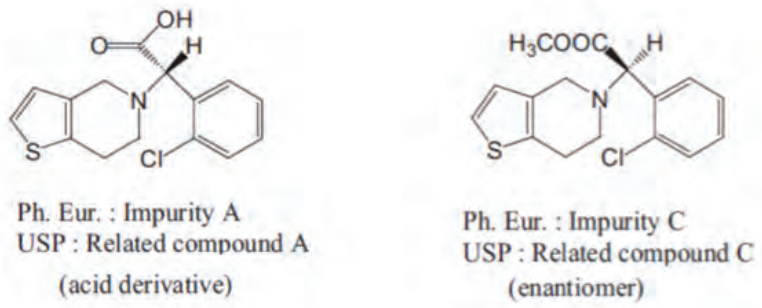
FIGURE 2



Clopidogrel Impurities

phase is physically stable and safer for administration. The elimination of solvents from the formulation reduces injection site irritation and is more acceptable for pediatric products; and the minimization of surfactants improves the safety and chemical stability of the resulting nanoemulsion formulation. Ascendia has used its EmulSol technology to formulate its lead pipeline product - ASD-002 - a novel injectable form of the anti-thrombotic drug clopidogrel.

CLOPIDOGREL

Clopidogrel, first approved in 1997, was co-developed and co-marketed (as Plavix®) by Bristol-Myers Squibb and Sanofi. Clopidogrel is one of the leading anti-thrombotic drugs in use today, and as recently as 2011 was the second best-selling drug product in the world, achieving over $7 billion in sales that year.

Clopidogrel is indicated for Acute Coronary Syndrome (ACS), and also following recent myocardial infarction, stroke, or in established peripheral arterial disease. In particular, ACS refers to unstable angina or when blood supply to the coronary arteries becomes suddenly fully or partially blocked (ie, heart attack). When a patient presents with a suspected coronary event, a 300 to 600 mg loading dose of clopidogrel is frequently administered. However, the only commercially available dosage forms of clopidogrel are oral tablets in 300 mg and 75 mg strengths - not ideal for administration in an emergency setting. Also, when delivered orally, there is a significant delay in the time required for the medicine to become effective - although clopidogrel is rapidly absorbed, the time to reach peak concentration and therapeutic effect can require several hours. Therefore, in an acute, emergency setting, a more rapidly acting, injectable clopidogrel dosage form is desirable.

The barrier to developing such a product is due to clopidogrel's challenging solubility, physical form, and chemical stability properties. Clopidogrel is a weak base with a pKa of 4.5, and it is practically insoluble in water at neutral pH (the oral tablet composition uses the bisulfate salt form of clopidogrel, which is soluble at gastric pH, but not suitable for injection). Clopidogrel free-base is a semi-solid, viscous, oily form, thus presenting difficulties in storage, dispensing, and processing. Moreover, the free-base form is chemically unstable and undergoes both hydrolysis and oxidation. In addition, clopidogrel is a chiral molecule: only the s-enantiomer is biologically active, and chiral conversion to the r-enantiomer can easily occur in a liquid dosage form.

There have been development efforts to formulate and clinically test an injectable clopidogrel dosage form. Ligand licensed an injectable clopidogrel formulation (developed by Prism using Cydex's cyclodextrin-based technology platform) to The Medicines Company in 2011.[3] Other injectable formulations have been studied clinically.[4] And the patent literature also discloses attempts to formulate stable parenteral dosage forms.[5] However, despite the development efforts to date, and the

clear unmet medical need, an injectable form of clopidogrel has not been successfully developed and approved.

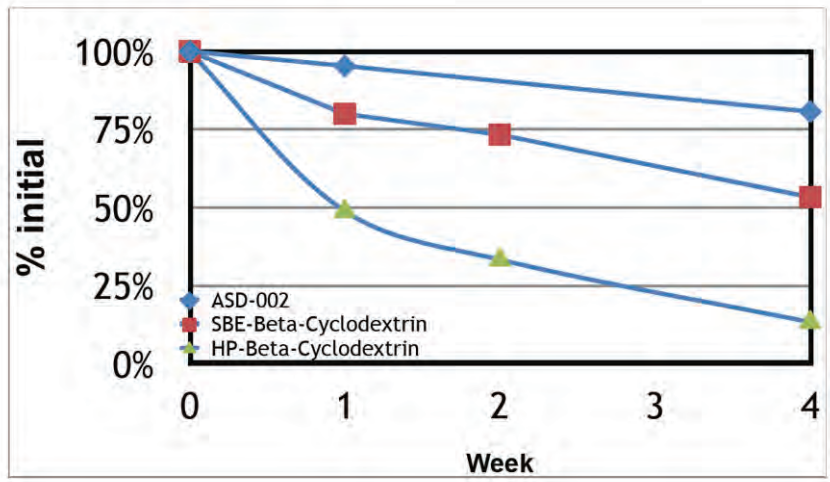
ASD-002: INJECTABLE CLOPIDOGREL

Using its EmulSol technology, Ascendia has developed a novel oil-in-water nanoemulsion formulation of clopidogrel. The goal of the development program has been to demonstrate successful formulation of clopidogrel free-base in a nanoemulsion suitable for injection, having acceptable chemical and physical stability properties. Because the formulation contains no solvent, the risk of injection site pain is greatly reduced. And, even though the free-base is poorly soluble at plasma pH, when contained in the oil phase of the nanoemulsion, the clopidogrel drug substance becomes much more soluble as shown in Table 1.

The ASD-002 nanoemulsion is prepared by high-pressure homogenization using Ascendia's proprietary excipient blend. The mean droplet size for the clopidogrel nano-emulsion is approximately 200 nm as shown in Figure 1.

Another challenging aspect of this development program is the demonstration of chemical and physical stability.

FIGURE 3



Assay of ASD-002 Vs. Cyclodextrin Preparations After Storage at 60°C

Clopidogrel has several degradation pathways, including oxidation (Impurity A), hydrolysis (Impurity B), and chiral conversion (Impurity C) as shown in Figure 2. Ascendia has investigated the degradation pathways of clopidogrel free-base and clopidogrel bisulfate in aqueous solution, and developed stability indicating analytical methods.[6]

Ascendia has demonstrated physical stability of the formulation by showing minimal change in oil droplet particle size following either autoclaving the formulation, or a freeze-thaw cycle for the formulation - the mean particle size remains a consistent 200 nm. Chiral conversion to the r-enantiomer is the predominant chemical impurity. Ascendia has shown in accelerated stability studies that chiral conversion is kept within USP limits for sufficient time to provide a commercially acceptable product shelf-life. ASD-002's stability profile has been compared to other aqueous-based liquid formulations (eg, cyclodextrin-based liquid forms) of clopidogrel and demonstrates superior chemical stability with respect to all three major impurities - chiral degradation, oxidation, and hydrolysis (Figure 3).[7]

CONCLUSION

Nanoemulsions are useful in developing liquid formulations of poorly water- soluble drugs for oral or injectable administration. Oil-in-water nanoemulsions can also be used to stabilize drugs that undergo hydrolytic and oxidative degradation. These challenges have prevented development of a soluble, stable form of the anti-thrombotic drug

clopidogrel in a suitable parenteral dosage form, despite the significant unmet medical need for such a product in treating acute coronary syndrome.

Using its EmulSol technology, Ascendia has developed a novel oil-in-water nanoemulsion formulation of clopidogrel whereby the free-base form of clopidogrel has acceptable solubility in the oil phase, and is protected from chemical degradation. Ascendia continues to explore further development and partnering opportunities for this unique product. ◆

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BIOGRAPHIES

Troy M. Harmon joined Ascendia in 2014 as Vice President, Business Development. Mr. Harmon earned his Bachelor of Science degree from the University of Kentucky, where he was elected to Phi Beta Kappa and received the University's first prize for undergraduate academic research. Mr. Harmon also earned a Master of Science degree in Physical Chemistry from Cornell University and a Master of Business Administration degree from Villanova University. Prior to Ascendia, Mr. Harmon was Vice President, Business Development at Eurand, where he was responsible for Eurand's business development, licensing, alliance management, and commercial sales efforts in North America. Prior to Eurand, Mr. Harmon was Director, Business Development at Delsys Pharmaceutical; Director, Business and Product Development at FEI Technologies; and a Sr. Scientist at Summit Technology.

Dr. Jingjun Huang founded Ascendia in 2012 after 15 years of pharmaceutical R&D and management experience at Pfizer, Baxter, AstraZeneca, and most recently Roche. Dr. Huang earned his PhD in Pharmaceutics from the University of the Sciences in Philadelphia. He has led the formulation development efforts for the successful transition of several oral and parenteral dosage forms from discovery through formulation, manufacturing, technical transfer, and ultimately commercialization. Dr. Huang's research interests are centered on improvement of solubility and dissolution, and controlled delivery of poorly water-soluble drugs through nanoemulsion and amorphous solid dispersion technologies. He has been a reviewer for the Journal of Pharmaceutical Sciences, International Journal of Pharmaceutics, Journal of Controlled Release, Drug Development and Industrial Pharmacy, PDA Journal of Pharmaceutical Science and Technology, Molecular Pharmaceutics, and Pharmaceutical Research. Currently, he is a member of American Association of Pharmaceutical Scientists (AAPS) and American Chemical Society (ACS).

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Quality-by-Design: The Good, The Bad, The Inevitable

By: Michael Lowenborg

INTRODUCTION

To bring new ideas and innovations into the real world, science has to be made into something tangible. While that's the fundamental mission for many pharmaceutical companies, that's exactly where many drug development programs fall short - in the actual formulation, engineering, and production of new products. This is evident as the US Food and Drug Administration (FDA) continues to emphasize the "modernization of the regulation of pharmaceutical manufacturing and product quality." Poised to be the key driver of that mission is Quality-by-Design (QbD).[1]

With proportionately smaller shares of product development investments going toward actual formulation and production, it's all too easy to overlook the processes that are so critical to a product's downstream approval and long-term market viability. A focus on upstream investigation to ensure the integrity of drug products is what QbD is geared to instill in development programs. In essence, QbD can be interpreted as a way to maximize time and cost savings by better understanding the components and processes necessary to optimize a drug product's safety, efficacy, and quality at every stage in development.

UNDERSTANDING QBD

While the concept of QbD originated in the early 90s, it's a much more recent phenomenon for pharmaceutical companies, having only been adopted and refined for end-to-end drug development programs throughout the past decade. Today, confusion exists as to whether or not the FDA expects QbD to become a standard part of all submissions in the near future. In short, the answer is yes; the FDA is demanding that components of QbD be provided in all submissions. Already, generics companies have felt the pressure as the FDA has moved beyond evaluating mere equivalencies of generics to reference drugs, especially as products increase in design complexity.[2]

The FDA continues to prepare inspectors to more capably accept and review QbD submissions, and there is an expectation that QbD will become standard practice for generics makers. In fact, the majority of ANDAs now include multiple QbD elements. At a presentation at the International Forum Process Analytical Chemistry meeting in January 2013, Daniel Peng, PhD, noted that in June and July of 2012, only about one in four ANDA filings contained multiple QbD elements, while more than 80% did at the time of the presentation.[3] As of January 2013, ANDA applicants are being "strongly encouraged" by the FDA to apply QbD - deficiency letters will now explicitly cite the lack of QbD.[4]

While the rise of QbD is certainly evident and perhaps more pressing for generics, the number of new drug QbD submissions has also increased steadily, with just one in 2005, seven in 2008, nine in 2011, and six in less than the first half of 2012.[5] While the FDA has noted lapses in QbD filings, both the FDA and drug makers are looking to normalize the application of QbD in submissions. While

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QbD does not directly reflect a change in regulatory requirements, it can provide opportunities for more flexible approaches to meet evolving regulations.[6]

From the FDA's standpoint, QbD represents a schema or thought-process behind the development and manufacture of a product and adds a measure of accountability. The FDA wants drug makers to demonstrate that they've challenged raw materials and processes to ensure products are performing not only as intended, but as optimally as possible given the inputs. For example, the FDA wants to know: How has the formulation been deconstructed and reconstructed? Are these ingredients put together in the best way possible? What are the minimum/maximum target values set before testing, and how has the product fluctuated within those minimum and maximum values when different processes are used? QbD answers these questions.

THE FOUR PILLARS OF QBD

1. Define the Product Design Goal

Outline the quality target product profile (QTPP), and identify all the critical quality attributes (CQA) for the product. The QTPP includes factors that define the desired product, including the intended use of a product, route of administration, delivery system, dosage form, and dosage strength, among others. A CQA is "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality."[7] By conducting experiments on different formulations (eg, gels, ointments, sprays) to characterize a substance's solubility, compatibility, stability, etc, the QTPP and CQAs provide a framework for product design and understanding.

2. Discover the Process Design Space

ICH Q8 defines design space as an "established multidimensional combination and interaction of material attributes and/or process parameters demonstrated to provide assurance of quality." Critical process parameters (CPPs) are identified by determining the extent to which any process variation can affect the quality of the product.[8] By defining the design space, issues can be anticipated and better control of the process can be achieved. Actual experimental data, product experience, or literature guidance can be used to define the extremes of the parameter sets to be refined.

3. Define the Control Space

Based on the process design space, a control space can be defined. This enables an understanding of processes in a way that ensures product quality from known variability of the production process. This approach will keep multifaceted production processes under tighter control. To illustrate the concept of a control space study, think of a reference product dataset with tightly clustered data points that represent the output of a tightly controlled process. Plotting the output of a process and comparing it to such a reference will indicate whether a process is in control. One technique to help avoid disparities is to conduct a design of experiments study on a product in the development stage. Considerable wasted effort can be eliminated, and root causes of unexpected adverse outcomes can be found sooner with such an approach.

4. Target the Operating Space

The operating space is the best set of parameters, determined statistically, which enable accommodation of any natural variability in CPPs and CQAs. For generics, the operating space should be within the control space and should allow a reference product to be tested with the same set of parameters. For new products,

the operating space should be within the design space and compliant with regulatory guidelines. Innovators can gain a competitive advantage by thoroughly exploring the design space, including testing numerous batches of formulations to truly refine their product.

THE CASE FOR QBD

While regulatory agencies anticipate that products will be developed using QbD, drug makers should see it as more than regulatory decree; QbD is a methodology that formalizes product design, automates labor-intensive testing, and simplifies troubleshooting. By taking a systematic approach to understand the compatibility of a product with all of the components and processes involved in the manufacture of the product, drug makers are better equipped to safeguard product integrity.

Rather than conventional end product testing that relies on reproducibility, which can be costly on both ends of a development pipeline, QbD compels drug makers to assess processes and components earlier to grasp how they influence quality, safety, and efficacy. In short, QbD calls for thorough early investigation and more capable follow-through. On the commercial end, QbD ensures that the more information generated about the influence of a component or process on a product's quality, safety, or efficacy, the more business flexibility is created. QbD also represents a bridge between developers and manufacturers, and better alignment among all parties involved in the design of a new drug - from concept to commercialization - to make the development process a concerted effort.

QbD is essential to preformulation and formulation stages, in which the goal is to identify risks - from environmental factors to shelf-lifespan - that may affect the final drug product. The extent of examinations is variable at this stage. For example, informal stability testing may also take place to evaluate packaging compatibility. Beyond physical testing, chemical and microbiological tests may also be conducted. By understanding how API degradation, mixture uniformity, viscosity, etc, may affect a product's performance downstream, the in-process testing that QbD necessitates serves as both a framework for in-process improvement and future-proofing.

Consider the fallout of an out of specification (OOS) result: Insufficient data and/or in-process testing can lead to a seemingly endless search for the root cause(s). In fact, even a four- to nine-fold increase in testing could be required to remediate an OOS event.[9] Potentially, huge external costs during and after product development can also come as a result of:

- Delayed product launch and/or approval
- Failure to achieve or maintain regulatory compliance, resulting in severe actions, such as consent decrees
- Misused raw materials and redundant manufacture of scrap batches
- Suboptimal manufacturing processes, and the resulting investigation and remediation when issues and deviations are found[10]
- Failure to successfully scale up an end product

The proactive investigation and intervention QbD incorporates can yield significant business benefits, including:

- Fewer lost batches, which could cost $250,000 to $500,000 per batch
- Fewer manufacturing deviations, saving hundreds of hours and $10,000 to $15,000 per deviation
- Faster time to market and more reliable supply, when each day on

the market could mean $100,000+

- Fewer inspections of manufacturing sites
- A many-fold increase in ROI via cost savings and improved revenue

QBD ISN'T A QUICK FIX

While QbD's downstream time and cost savings have proven significant for many development programs, there is still an initial investment to implement QbD. In general, developers are focused on getting their product to a manufacturing plant as early as possible. But implementing QbD - and designing and executing studies, then analyzing them to make sense of findings - can take up to 4 months or more before manufacturing. As off-putting as this is for many developers, there are other factors that compound the challenge.

QbD can be especially difficult to implement across the board when operations are fragmented, either geographically or functionally. Even when a QbD system is in place, technology, and knowledge transfers can be problematic when new personnel are being introduced without any prior guidance, for example, when a product is making the transition from development to manufacturing. While QbD is a systematic approach and can be implemented systematically into business operations, it's important that everyone involved with a research program understand the concept of QbD before implementation. Putting QbD practices in place is only the beginning - the entire line of personnel with hands on a product must demonstrate a sustained commitment to continuous improvement that QbD demands.

QbD requires an investment of time and labor at each stage of development. Moreover, QbD necessitates adequate technologies and expertise be in place. Additionally, there are secondary matters to appraise (eg, data management, regulatory/filing preparation, internal management buy-in, and governance). While some companies may feel the pressure to get on board with QbD, careful consideration and planning are vital. As one consultant put it, "QbD can be significantly less daunting if the organization understands clearly what is most important, where there are critical gaps and what must be done to close them."[11]

Within the FDA, reviewers vary in levels of understanding and adoption of QbD. While that looks to become more standardized, interactions with the FDA may still pose problems, as with any new practice that involves unique principles and lexicon. The three following observations were made in a recent QbD-based ANDA filing that highlight issues with the adoption of QbD:

1. Exhaustive information was presented with no justification or interpretation (no conclusions) of data
2. Basic QbD terminology, such as CQAs, CPPs and, in particular, process design space, was misused
3. Prior knowledge was often presented without necessary context or justification for its use[12]

CONCLUSION

From scientific and business standpoints, the case for implementing QbD is becoming stronger. QbD is a form of investment that certainly takes time and money to establish, but the ultimate costs are negligible and enable more efficient use of development funds. QbD is not just a methodology for mitigating risk and variability - it's a viable means to discover insights upstream throughout your development process. It's evident that the FDA sees QbD as a way to optimize the quality of drug products for everyone involved. From developers and

manufacturers, to regulators and patients, QbD drives more consistent, high-quality drug products that meet safety and efficacy requirements. Today, the FDA expects the following QbD components in all submissions: the QTPP; lists of CQAs, CPPs, and critical material attributes of the drug and excipients; and the control strategy that ensures the product meets its predefined objectives.

While QbD can establish singularity in the development of a drug product, adopting QbD can prove overwhelming and, if misapplied, inefficient and expensive. A knowledgeable partner - one that has demonstrated successful QbD implementation - is a must for companies looking to adopt QbD. ◆

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BIOGRAPHY

Michael Lowenborg is Manager of R&D Formulation and Process Development, DPT Laboratories. With nearly 20 years of experience in the industry working on semi-solid and liquid formulations, primarily topical skin treatment products, he has been with DPT Laboratories for more than a decade. Before joining DPT, he served as development chemist for Estee Lauder and as formulation scientist for Avon. Mr. Lowenborg frequently speaks at industry events and presents on the implementation and use of QbD. He is a member of the AAPS as well as the Society of Cosmetic Chemists. Resources authored and presented by Mr. Lowenborg, including white papers, articles, webinars, and more, are available at dptlabs.com/resource-center.

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RESEARCH & INNOVATION OF AUTO INJECTORS TO ENHANCE PATIENT COMPLIANCE

The enhanced features and convenience provided by auto injectors has increased patient acceptance towards such self-injection devices in recent years. With a wide range of auto injectors already on the market and more entering soon, patients are now more familiar with this type of technology and expect devices to offer key fundamental features such as dose accuracy, ease-of-use, safety, and related feedback systems.

FUNDAMENTAL FEATURES

While designing such devices with the end-user in mind has always been part of most auto injector developments, the traditional emphasis on this relatively new medical device was more focused on features and related specifications. These features would be the incorporation and realization of the pharmaceutical companies' original injection specifications into the device's mechanical mechanisms and exterior design. For example, injection time would be dependent on the spring force or adjustments made to the power pack built into the device, whereas feedback forms can be the result of intricate component interactions before, during or after an injection. Other details including information on the primary container, injection depth, viscosity range, and more, were some of the key inputs behind the design of the auto injectors at the time. Today, these features have become mandatory benchmarks upon which new designs are realized, but now with an added emphasis on usability and human factors engineering (HFE) to help enhance the patient experience and to support compliance.

R&D WITH USABILITY IN MIND

With numerous biologics coming to market, timeline is especially critical to pharmaceutical companies when it comes to developing competitive combination products such as auto injectors. As the development of customized auto injectors can often take many years before launch, device partners are under more pressure to innovate technologies and manufacturing processes either to help shorten time-to-market or to be prepared for the pharmaceutical company's future portfolio needs. Since auto injector products are usually custom-built projects tailored to the drug's therapeutic specifications and targeted user preferences, considerations with regards to HFE and usability compliance are typically implemented during development stages. To stay proactive in providing patient-centric solutions, device manufacturers now need to examine usability studies as early as possible during R&D stages and innovate accordingly.

Figure 1. SHL's Amber is an intuitive 2-step auto injector designed with a unique ergonomic exterior.

An experienced device partner should already have a team of industrial designers skilled in optimizing product architectures while complying to design processes. Optimization considerations include integrating safety features, controlling costs, use of enhanced ergonomic designs and so on. It used to be the case that device components were added whenever a new function or feature was desired. Now, designers have to continuously research and innovate to minimize and simplify features for ease-of-use and manufacturability even before a pharmaceutical customer comes knocking on the door with a request. These designs should be ready to comply with standard HFE and usability guidelines and be reflective of basic usability studies conducted. To achieve this, the ideal device partner needs to have a strong R&D team and sufficient manufacturing capabilities in-house for support. By having both under one roof, conceptual designs can be quickly realized through prototype production and verified for manufacturability.

For example, as part of an internal user study, the mechanisms of a specific proven platform (disposable auto injector with single dose and no button) was placed inside 5 other specially designed prototypes with unique cap, body and rear cap. The purpose of the study was to perform qualitative research and observe the relationship between different device designs and the

user's perceptions, with the ultimate goal of further improving the current mechanism and for future design reference. Since the study was conducted for R&D and not intended for a device with a specific drug, a generic group of users unfamiliar with auto injectors was chosen instead of a targeted patient group. Including the original auto injector, a total of 6 devices were made available during this structured study. The results provided design insight into various aspects of usage including ways users removed the cap, how the device body was gripped, angles at which the device was held during injection, activation sequences and more. The users were also interviewed to gain a thorough and in-depth understanding of their behaviors, all of which were grouped and analyzed accordingly to help establish new design guidelines that were communicated back to the designers and engineers.

The investment in similar internal programs reflects a device manufacturer's dedication to partake in the on-going goal of designing intuitive auto injector devices in addition to just technical implementations. However, the latter example is for internal R&D only and is quite different from the human factors design processes required during an actual development program with a specific drug.

BEYOND THE DEVICE: TRAINERS AND LABEL INNOVATIONS

A medical device such as an auto injector can go through rigorous usability studies and embody as much human factors engineering as possible, yet still potentially result in patient's mishandling any device. Aside from user interface related causes, this can be the result of anxiety during injection and/or miscomprehension of the instructions included with the device. Traditional supplementary tools such as Instructions for Use (IFUs) can often consist of comprehensive information, pictures, icons and diagrams that the patient may not be able to fully follow at first use, especially when under stress. To provide more education and guidance for these patients, tools such as needle-less trainers and enhanced labels are now often encouraged for most device programs; especially those that are single use disposable devices.

Figure 2. Needle-less Trainers allow users to familiarize with the injection process and also help reduce anxiety.

Auto injector trainers generally simulate the look and feel of the actual device, but without any drug or needle inside. For many patients who are used to receiving treatments administered by trained healthcare professionals at clinics or hospitals, the idea of unsupervised self-injection can be intimidating. Trainers allow them to practice at home without the risk of potential injury and thus helps to give patients a clear understanding of how a device should function, relieving some potential anxiety. Even just one unsuccessful attempt can prompt the patient to develop concerns about future injections and may have a significant impact on their compliance with regards to the drug and device itself. Developing trainer devices has thus become an essential component of device programs, and a number of device suppliers have made it a goal to assist their pharmaceutical partners in providing more comprehensive toolkits for patients.

In addition, with digital technology and electronic devices quickly advancing and readily available around us, device labels can now be much more robust than just a sticker with mainly textual information. One example is a near field communication (NFC) integrated label, which allows the individual device to have its own digital signature. Reading the signature with a smartphone can give patients access to a range of alternative tools such as video instructions, voice-guided steps and treatment records, all with the goal to enhance patient education and compliance. These functions would have been otherwise difficult to build into the device without a significant impact on cost.

A NEW ROLE FOR DEVICE MANUFACTURERS

The self-injection device market has quickly matured in recent years and device designs are now often driven by patient usage behaviors and compliance. As a device manufacturer, it is no longer sufficient to directly translate the technological aspect of the specified design input requirements into a device. Both new and existing pharmaceutical players now expect that a device partner can offer not only a knowledge base but the proactive application of the data in their R&D innovations and available device platforms. This is especially essential for pharmaceutical companies that are developing an auto injector product for the first time. This way, the pharmaceutical companies can not only leverage the key established capabilities, which are still the foundation of all development projects, but also benefit from the past project experiences as well as the device manufacturer's on-going evolution to improve device usability and to provide support.

Figure 3. Looking at innovative technologies in areas such as labelling can help the patient experience.

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Solumerized™ Trans-Resveratrol: Bridging the Bioenhancement Gap to Drug Delivery Between Pharmaceuticals & Dietary Supplements

By: Amir Zalcenstein, PhD, Galia Temtsin Krayz, PhD, and Sabina Glozman, PhD

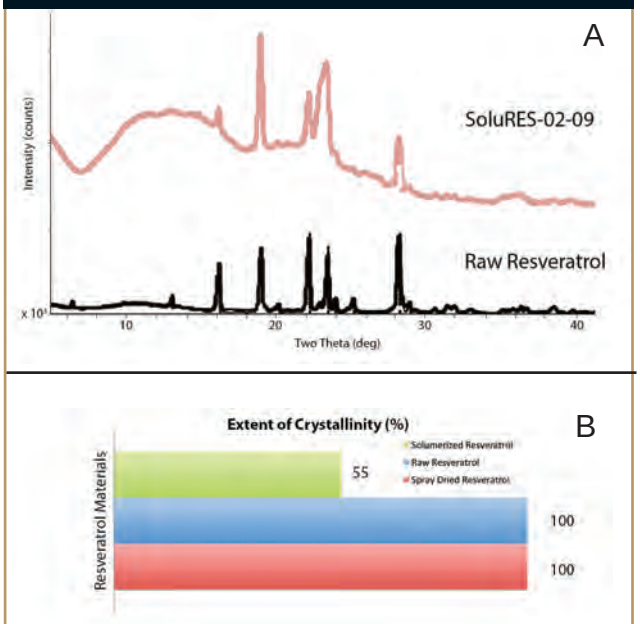
ABSTRACT

Dietary supplements have been slowing the utlization of cutting-edge drug delivery technologies, mostly as a result of the high unit costs these platforms confer upon the finished products. SoluBest has worked to modify its platform to formulate low-solubility dietary supplements and reports that the resulting products can be competitive in this highly price-sensitive market.

INTRODUCTION

There is no doubt that dietary supplements have become a household item, used by people throughout the world to augment their health and sense of well-being. Indeed, many of the supplements marketed are backed by credible scientific data attesting to their efficacy and ability to prevent the deterioration of health. However, drug delivery technologies have not yet made significant headway in this market, primarily due to cost/benefit considerations. In a market in which cost is a key differentiating factor, supplement manufacturers have been reluctant to invest in cutting-edge delivery technologies that would significantly increase their unit costs; on the other hand, advanced drug delivery platforms are rarely designed with reducing unit costs in mind. The result is that apart from some non-proprietary micronization techniques, supplements - even those with low bioavailability - are rarely formulated using the technologies that can truly boost their performance. A new generation of delivery technologies, exemplified in this article by SoluBest's Solumer technology, is poised to change this by enhancing the bioavailability of numerous active ingredients using easily formulated, proven, and perhaps most importantly, cost-effective delivery technologies capable of significantly enhancing the bioperformance of

FIGURE 1A&B



Decreased Crystallinity Exhibited by Solumerized Resveratrol
A) X-Ray Diffraction (XRD) analysis of SoluBest's Resveratrol formulation vs. raw Resveratrol. While both materials exhibit peaks at the same locations, those of the Solumerized Resveratrol are markedly widened, indicating increased amorphosity (eg, defects in the crystalline structure).
B) Analysis of XRD data showing reduction in crystallinity is attributable to Solumerization. XRD data was collected from different samples, and calculated to reflect % crystallinity. While raw Resveratrol and spray-dried Resveratrol maintain 100% of their crystal structure, Solumerization accounts for a significant 45% decrease in crystallinity. This characteristic is stable over time (3 years).

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In this article we will discuss the example of Resveratrol, a supplement with a solid body of scientific data attesting to its efficacy in enhancing lifespan and treating a variety of medical conditions (heart diseases, diabetes, cancer, etc), which yet remains short of its true market potential due to stability, bioavailability, and cost issues.

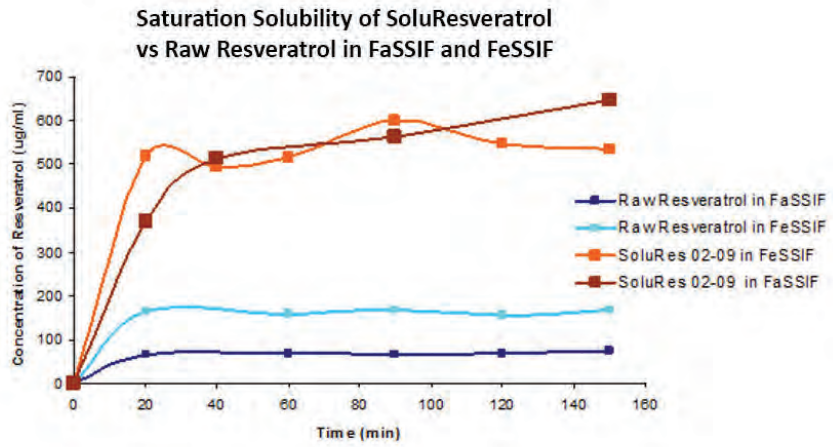
RESVERATROL: STILL AN ANTI-AGING PARADIGM CHANGE

Resveratrol is a super-antioxidant, which helps combat heart disease, diabetes and cancer, helps to lower blood cholesterol, and is useful in diseases accompanied by inflammation. Resveratrol was discovered in the late 1990s as part of the investigation into the French Paradox - the discrepancy between the French's low rate of cardiovascular diseases and the typical French diet, which is high in saturated fats. Focusing on components present in red wine, researchers isolated Resveratrol and identified its beneficial effects on the health and life-prolonging activities in animal models. It has been also determined that Resveratrol exerts these effects via activation of Sirtuin proteins, molecules that prevent cellular aging and inflammation.[1] Since then, efforts have been made to translate these findings from animal to human clinical models, while various companies have tried to tap the commercial potential of this promising supplement.

As is the case with all other actives, the beneficial effects of Resveratrol (and of active ingredients in other supplements) are governed not by its dose strength, but by its actual bioavailability. For Resveratrol, an unstable molecule with extremely low solubility, delivery into the bloodstream is a significant challenge. To overcome its inherent bioavailability issues, Resveratrol is commonly marketed in dosages up to 500 mg per capsule or tablet. Different products contain 30% to 99% pure Trans-Resveratrol, with higher purity commanding higher prices. However, a number of significant obstacles stand between raw Resveratrol and a highly bioavailable supplement - even one that contains a high dose of raw material.

First and foremost, Resveratrol has been shown to be quite unstable. Any preparation of Resveratrol typically contains the two common forms of the molecule: the cis- and the Trans-Resveratrol variants, with the cis-variant

FIGURE 2



Increased Solubility of Solumerized Resveratrol (SoluRes) Compared to Raw Resveratrol in Simulated Gastric Fluids
Simulated Gastric fluids are composed of the same ingredients one would find within the active human gut - ions, enzymes, bile, and stomach fluids etc. Fed and fasted simulated gastric fluids differ in the acids amount and concentration of fats added to simulate a fully digested meal. Compare dark blue (Raw Resveratrol vs. SoluRes in FaSSIF, simulated FASTED Intestinal Fluid) to dark brown. Increase in dissolution is over 5x. Compare light blue to light brown (Raw Resveratrol vs. SoluRes in FeSSIF, simulated FED Intestinal Fluid). While Resveratrol solubility is enhanced in the high fat environment, increase in dissolution remains at least 4x. SoluRes has NO food effect.

TABLE 1

Sample	T_{melt} (ºC)	$\Delta H(^{o}_{melt}$ (J/g_{drug})*
Resveratrol starting material	267.4	253.6
SoluRes -02-09	196.7	9.32

Modification of Resveratrol's Physical Properties Through Solumerization as Measured by Differential Scanning Calorimetry (DSC)
As can be seen, there is a significant reduction in both the melting temperature of Solumerized Resveratrol as compared to the raw materials, and a reduction in the energy required for melting (enthalpy).

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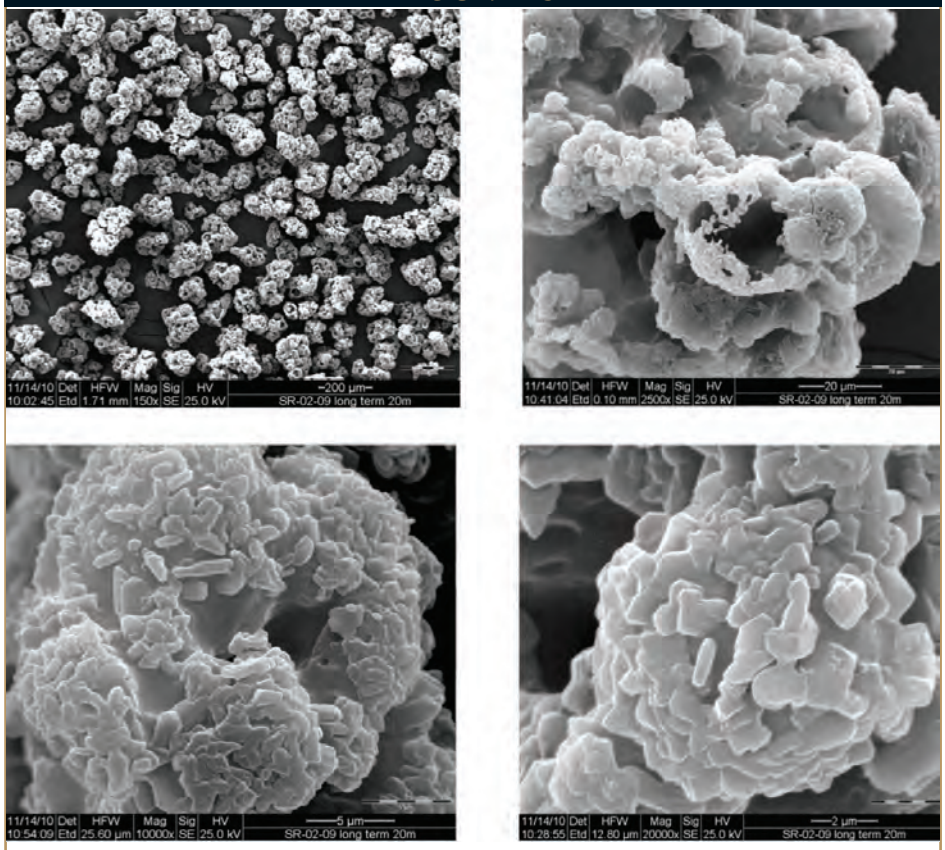
FIGURE 3



Electron Microscopy of SoluBest's Micro-Sized Structures Enmesh Nano-Particles of Resveratrol Embedded in Polymeric Matrix

Different magnifications of Solumerized Resveratrol (SoluRes) particles using a Scanning Electron Microscope (SEM) reveal a characteristic structure unique to the platform. Top left: aggregates of micro-sized particles form a fine powder; upon closer examination (top right) aggregates are shown to be composed of porous structures, allowing maximum surface area for a polymer-active matrix to interact with the adjoining medium. The Substructure of the matrix (bottom left, bottom right) shows Resveratrol crystals (0.5 to 5 microns) enmeshed in a polymer matrix.

being more stable than the trans-variant. This results in the rapid degradation of Trans-Resveratrol into cis-Resveratrol. Unfortunately, only the less stable trans-variant is biologically active. This degradation is rapid and well documented: Rossi et al. reported that there is a significant decline in the content of Trans-Resveratrol in a number of products during the products shelf-life - up to 55% less than the stated amount.[2]

Second, Resveratrol is characterized by low bioavailability, and only a small fraction of it reaches the blood. For example, Brown et al reported Cmax levels of Resveratrol following administration of 500-mg daily doses for a minimum of 21 days to be only about 43.8 micrograms per liter of blood.[3] When calculated together with the quantities of Resveratrol's most common metabolites, this amount rises to approximately 0.97 mg/L, equating to an extremely low rate of absorption. This extremely low bioavailability is a result of Resveratrol's hydrophobicity and highly ordered crystalline structure, which prevents its dissolution in the GI tract and subsequent absorption, as well as the rapid breakdown of the molecule in the liver after absorption (it is important to remember, however, that there is evidence that some of Resveratrol's therapeutic effects are actually exerted by its metabolites).[4] The issue is compounded by repeated observations that Resveratrol only has discernable effects if a consistently high level of blood Resveratrol is maintained.[5]

As noted previously, the most common approach has been to administer high amounts of Resveratrol in order to exert any biological effect. However, this approach is hampered by the unpleasant side effects exerted by the unabsorbed Resveratrol remaining in the GI tract, which increase as larger amounts of Resveratrol remain unabsorbed.[3,4]

Supplement manufacturers have attempted to solve these issues in a number of ways. The trans-to-cis transformation issue has been addressed by certain manufacturers by the introduction of synthetic 99% pure Trans-Resveratrol which is supposed to retain its stability significantly better than plant-derived variants. This approach, however, does little to improve the compound's inherently low bioavailability. To this end, certain manufacturers have attempted to enhance Resveratrol's solubility characteristics by converting it into micro-sized particles. While this approach undoubtedly results in a certain bioavailability advantage over the unformulated compound, an approach championed by the drug delivery company SoluBest manages to bypass all the obstacles noted previously using a focused formulation approach.

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TABLE 2

Data Source	Resveratrol dosage form	Dose mg	Cmax, ng/mL	Cmax/D 10^6/mL	AUC ng-hr/mL	AUC/D 10^6hr/mL
Solubest study	Solu-RSV suspension	500	**407**±247	**0.81**±0.49	**448**±334	**0.90**±0.67
Solubest study	Suspension, Sito	500	**71.9**±72.2	**0.14**±0.14	**108**±101	0.22±0.20
Boocock 2007	IR caplets, Royalmount Pharma	500	**72.6**±35.5	**0.15**±0.07	**224**	**0.45**
Brown 2010	IR caplets, Pharmascience Inc.	500	**43.8**±39.2	**0.09**±0.08	**175**±146	**0.35**±0.29
Nunes 2009	Trans-resveratrol capsules	500	**23.5**±7.4	**0.12**±0.04	**56**±35	**0.28**±0.18
Almeida 2009	Trans-resveratrol capsules	500	**24.8**±19.7	**0.17**±0.13	**32**±20	**0.21**±0.13

Comparison of the Relative Levels of Absorbed, Unmetabolized Trans-Resveratrol in Leading Resveratrol Bioavailability Studies to SoluBest's Results
SoluBest's approach shows a significant bioavailability advantage when compared to other Resveratrol formulations' bioavailability as reported in the literature. Generally, SoluRes exhibits a minimum 5x, and up to 9x enhancement of bioavailability over other leading brands.

A NOVEL DRUG DELIVERY PLATFORM APPLIED TO SUPPLEMENTS

Solumer, SoluBest's drug delivery platform manages to bypass the limitations posed by a wide spectrum of bioavailability- and stability-challenged compounds. It is amenable to a wide variety of oral dosage forms, yet remains a cost-effective alternative to other, less advanced formulation techniques.

Scientific Rationale

Bioactive substances can be classified according to their physical forms. Some are liquid (or dissolved in liquid) and can be administered orally or injected. Others are commonly solids, and these can be classified further according to the arrangement of the bioactive material's molecules. Thus, amorphous solids lack a crystalline structure, are dissolved readily in biological fluids, and hence tend to be highly bioavailable. On the other hand, commercially formulating amorphous solids can be extremely challenging as they tend to be quite unstable.

On the other end of the spectrum are the crystalline bioactive solids. These tend to be highly stable with generally very good shelf-lives, yet the crystalline structure that contributes to their stability also hampers their dissolution and results in relatively low bioavailability. As can be seen in Figure 1 and Table 1, SoluBest developed its Solumer platform with the intention of creating a semi-amorphous/semi-crystalline interim state that allows its formulations both to maintain stability and to be very soluble, leading to enhanced bioavailability.

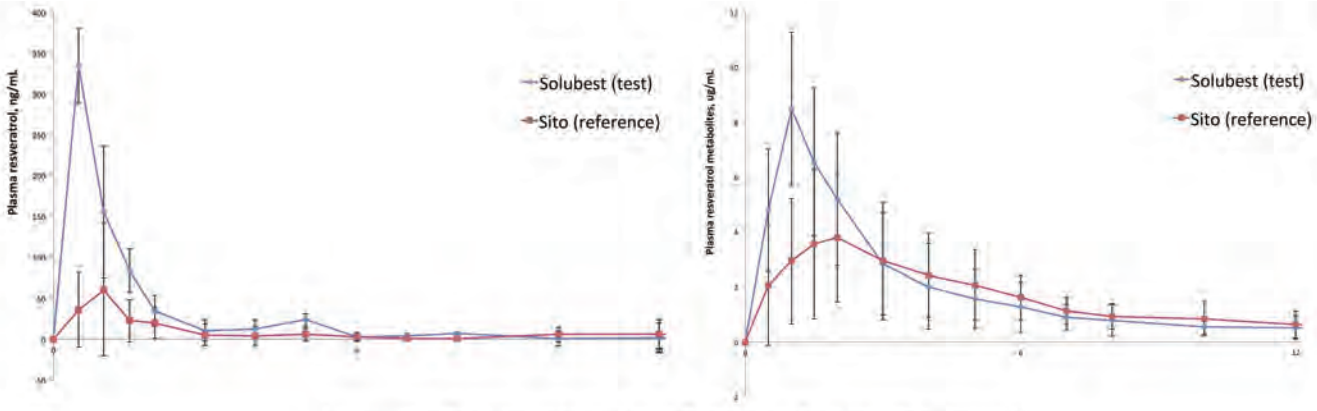
Solumerization achieves this by engineering particles consisting of a matrix using approved-for-food and safe-for-human use polymer building blocks together with the active compound, in this case Resveratrol. The polymers and active material are rapidly flash-dried, and during this drying step, submicron particles with a novel disordered semi-crystalline conformation are created. These particles are locked into the matrix, ensuring both enhanced solubility as seen in Figure 1 (due to the small particle size and the disordered crystal structure) and stability (due to maintenance of some degree of the same crystal structure). Moreover, as SoluBest's platform was developed with the elimination of the food effect in mind, the experiment depicted in Figure 2 shows equal solubility is obtained both in simulated fed and fasted conditions (see legend). As previously mentioned, fed conditions refer to a high fat meal prior to ingestion - a somewhat counterproductive approach in the case of Resveratrol.

Figure 3 shows the unique Resveratrol submicron structures created by the SoluBest's platform. When dry, the particles constitute a powder that could be easily converted into a variety of dosage forms familiar to consumers (capsules, tablets, and sachets). However, upon contact with gastric fluids, the unique structures readily disintegrate into highly bioavailable colloidal dispersions.

Clinical Trials

Critically, the real advantages of Solumer-formulated Resveratrol, SoluRes, are apparent when comparing its bioavailability to other formulations, and

FIGURE 4



Group	C_{max} ng/mL	AUC_{0-t} ng-hr/mL	Group	C_{max} ng/mL	AUC_{0-t} ng-hr/mL
SoluRes	407±247	448±334	SoluRes	9.0±2.6	29.3±14.2
Control	71.9±72.2	108±101	Control	4.6±2.5	25.5±14.3
P-value*	0.0005	0.0068	P-value*	0.0005	0.18

Results of a Two-Way Crossover Randomized Trial of Solumerized Resveratrol Versus Micronized Resveratrol (Control)
The trial was conducted in 2009 as a 1-day crossover experiment with a 2-week washout period: volunteers ingested 500 mg of Solumerized (SoluRes) or micronized Resveratrol (Control) and analyzed for blood Resveratrol and Resveratrol metabolite levels for 24 hours. Following a 14-day washout period, the formulations were swapped, and the patients were followed for a second 24-hour period of blood samples collection.
Left: Analysis of Trans-Resveratrol blood concentrations, where SoluRes shows a 6x increase in Cmax and 4.5x increase in AUC.
Right: Analysis of Resveratrol metabolites, where SoluRes shows a 2x increase in Cmax and approximately a 15% enhancement in AUC.

certainly to the commonly sold raw material.

First, the stability of the formulation plays a critical role once the formulation is ingested. Clinical testing using SoluRes indicates that the active ingredient reaches the blood in the form of Trans-Resveratrol or of its characteristic metabolites.

Moreover, the amount of Resveratrol actually taken up into the blood is far superior to any Resveratrol product currently available. In a two-way crossover randomized trial in 12 healthy volunteers, SoluRes showed a five-fold increase in Cmax (the maximum amount absorbed in the blood) of Resveratrol and its metabolites, compared to micronized Resveratrol.

Simply put, the 500-mg dose of SoluRes used in the trial exhibited bioavailability much higher than the equivalent amount of micronized Resveratrol, with Trans-Resveratrol bioavailability (after a single administration) reaching on average 407 micrograms/L. The Cmax values for SoluRes (407 micrograms/L of Trans-Resveratrol) were roughly five times the Cmax levels exhibited by the micronized control, and nine times higher Cmax as compared to the same dose administered in the study by Brown et al.[3] These results are even more striking given that in the study by Brown et al. daily doses of Resveratrol were given to the participants, and accumulation of the active compound and its metabolites in the body could have occurred. In contrast, a single dose of Reservatrol (SoluRes) was given to the patients in the SoluBest study (Table 2). Morover, when comparing the data collected by Brown et al., it is clear that the enhancement in bioavailability using the Solumer platform makes the amount administered on par with a 5-g daily dose. Extrapolating from these results to other products, we believe it is safe to conclude that SoluRes is bioavailable at least four to ten times more than unformulated Resveratrol following a single-dose administration; this advantage can be expected to be even more pronounced under conditions of repeated dosing.

BRIDGING THE BIOENHANCEMENT GAP TO DIETARY SUPPLEMENTS

While SoluBest's technology is one of a number of nano-formulation technologies capable of enhancing solubility, unlike other technologies, it was designed with mass market cost-sensitive products in mind. Thus, the platform utilizes off-the-

shelf polymers available in both food and pharma grades and uses spray-drying, a technology common to the food additive and supplement industry. The resulting powder is easy to handle and can be readily converted into tablets, capsules, and sachets. Moreover, as in the case of Resveratrol, in itself an expensive supplement (raw API can exceed $600/kg), the platform allows manufacturers to use less API while reaching the same efficacy.

It is estimated that using full-scale spray-dryers, combined with solvent collection and recycling, allows the platform to be implemented at a cost of less than $100/kg of API. While low-cost supplements probably benefit less from such the added price premium, the implementation of the platform toward supplements like Resveratrol with its concomitant enhancement in bioavailability results in a formulation with a unique value-for-money proposition. While the measure is unconventional, the cost per unit absorbed using SoluBest's platform is lower than almost any other Resveratrol product currently on the market. ◆

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BIOGRAPHIES

Dr. Amir Zalcenstein is an independent consultant specializing in NTE projects. Previously, he was Head of Business Development at BiondVax Pharmaceuticals, CEO of Amorphical Ltd. and SoluBest Ltd., and co-founded Targia Ltd., a reformulation company specializing in the CNS space. He earned his MBA from the Technion and his PhD from the Weizmann Institute.

Dr. Galia Temstin Krayz directs SoluBest's Formulation R&D, its analytical method development, process optimization, and scale-up. She earned her PhD in Organic and Material Chemistry from Ben Gurion University in Beer Sheva, Israel, and has specialized in self-assembly nano-delivery systems from Division of Material Chemistry, at the Chemical Department, at the University of Toronto, Canada. She has both academic and industrial experience in organic synthesis and process development of APIs in Perrigo (Chemagis, Israel).

Dr. Sabina Glozman returned to SoluBest after managing Biological Industries Ltd. since 2008. Previously, Dr. Glozman served as CEO at Vecta Pharmaceuticals and VP, Business Development at Protalix, among other companies. She has also founded a number of life-science start-up ventures, including Accelta Ltd. (a spin-off of from the Technion), as well as other projects from Ben Gurion University, the Israel National Institute of Biotechnology, and Haifa University. Dr. Glozman is a graduate of the Hebrew University in Jerusalem and has earned her PhD at the Weizmann Institute of Science' Neurochemistry Department.

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Vaccine Technologies & the Rationale for New Nanoparticle Formulations

By: Robert S. Becker, PhD, MBA, and Mark A. Mitchnick, MD

INTRODUCTION

Particle Sciences, Inc. (PSI) has developed a stable, hydrophobic nanoparticles technology that has the attributes of virus-like particles but with a much simpler architecture. They can be used to formulate vaccine antigens as particulates and link them to immunemodulators, such as TLR agonists at variable ratios and doses. This technology provides an efficient formulation platform for antigens and immunemodulators that can be optimized for both vaccine potency and safety profiles. The rationale for this vaccine technology builds on several of the major vaccine developments of the past 20 years that leverage the physicochemical attributes that the immune system uses to recognize microbes, leading to robust protective immune responses.

IMMUNE RESPONSES TO MICROBES

Two important vaccine advances have been the development of nanoparticle-based vaccine formulations and the identification of unique microbial products that are agonists for immunologic receptors: virus-like particles (VLPs) or nanoparticles, and Toll-Like Receptor (TLR) agonists, respectively.[1-3] The immune system continuously screens for and interacts with microbes, identifying them as foreign and targeting them for immune responses. The immune system has evolved to use these unique physical and chemical attributes, TLRs for instance, to recognize microbes and specifically respond with protective responses.

Bacteria and viruses, in essence, are naturally occurring micro/nanoparticulates that produce and are decorated with TLR agonists and assorted molecules, some of which are protective antigens. When antigen-presenting cells (APCs) of the innate immune system interact with the microbes' particle/TLR agonist structures, the APCs are stimulated to internalize the particles into endocytic vesicles and process them for immune presentation. APCs far more efficiently recognize and internalize these particles compared soluble molecules. The presentation of internalized antigens by APC involves processing the protein antigens into peptide fragments that bind to Major Histocompatibility Complex (MHC) proteins expressed on their surfaces. APCs interacting with microbes are also directly stimulated by the microbes' TLR agonists and respond by producing immunestimulatory signals, like co-stimulatory cell surface molecules and secreted cytokines that stimulate surrounding T and B lymphocytes.

Antigen-specific T lymphocytes recognize the presented antigen fragments on APC via their T cell receptors and are stimulated by APCs' co-stimulatory signals and cytokines. These stimulated T lymphocytes then proliferate, expanding

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their numbers, and differentiate to carry out cytotoxic or regulatory functions. Cytotoxic T lymphocytes kill surrounding cells that are acting as hosts for microbes, enabling the propagation of microbes, like viruses. The regulatory T lymphocytes express immunostimulatory molecules on their cell surfaces and secret lymphokines that simulate and regulate other cells, like B lymphocytes and other T lymphocytes.

B lymphocytes recognize the unprocessed forms of antigens on the surface of the microbes via their antigen-specific antibodies expressed on their cell surfaces. Microbes, which are particulate, can be especially stimulatory for B cells because they have multiple copies of antigens arrayed on their surfaces, which will cross-link the antigen-specific antibodies on the surface of B lymphocytes. This antigen-mediated cross-linking of B cell surface antibodies, the T cell-produced lymphokines and cell-surface signals, and the APC-produced cytokines cooperatively stimulate B lymphocytes. These stimulated B cells respond by proliferating to expand their numbers and to differentiate in plasma cells: the cells responsible for secreting antigen-specific antibodies that protect us from these infecting microbes.

These fundamental, natural immunological processes have evolved to efficiently interact with and recognize microbes, and they explain why the original crude vaccines composed of killed or attenuated whole cell bacteria and viruses have been very potent immunogens/vaccines: they are essentially particulate vaccines.

MODERN VACCINE FORMULATION TECHNOLOGIES

Understanding and taking advantage of these natural processes has become increasingly important as vaccine development has progressed toward creating biopharmaceutical products composed of highly defined recombinant proteins and synthetic molecules as vaccine antigens. Though these well-characterized, purified molecules are known protective antigens, they have routinely been poor immunogens/vaccines, lacking immune potency and immunogenicity because they no longer have the physical architecture of particles and *in situ* TLR agonists that differentiate and identify foreign microbes for the immune system. It has become important that modern biopharmaceutical vaccines be rationally designed to have the chemical and physical attributes that distinguish microbes for immune responses.

TLR AGONIST & ADJUVANTS

To improve the immunological potency of modern prophylactic and therapeutic vaccine antigens, alternative adjuvants and formulations have been pursued for more than 20 years. Many, if not most, of the active components of these adjuvants have been found to be TLR agonists.[2,3] These agonists are, or mimic, the components of microbes that are not produced by eukaryotic cells and so act as distinguishing markers for microbes. These components are, among others: LPS for which a modified form known as monophosphoryl Lipid A (MPL) has been developed and approved as a human vaccine adjuvant; flagellin, which is the monomeric protein that multimerizes to form the bacterial motility organ flagella; unmethylated CpG sequences, which are typical of prokaryotic DNA, single-stranded RNA sequences that are viral-like; and PAM_3cys/PAM_2cys, which is a lipid structure attached to some proteins exclusively in prokaryotes. However, when simply mixed with soluble purified antigens, these adjuvants/agonists typically require high adjuvant doses to be effective (Figure 1). At these high adjuvant

doses, TLR agonists disperse and systemically activate APC to secret cytokines, which results in an increased frequency of fevers and serious adverse responses in vaccinated individuals. In natural microbe-immune system interactions, the TLR agonists are present in very low doses and are physically associated with the particulate structure of the microbes. In this circumstance, TLR agonists interact and stimulate immune responses in a very localized and microbe-specific fashion. Thus, it's not surprisingly that the physical linkage of these TLR agonists to the vaccine antigens has been demonstrated to significantly reduce the required dose of TLR agonists needed as an adjuvant (Figure 1).

Linkages between TLR agonists and antigens have to-date been covalent in nature.[4] As an example, CpG adjuvants, a TLR9 agonist, has been chemically conjugated to a number of antigens.[5-7] Similarly, agonists for TLR7/8, which mimic to single stranded viral RNA sequences, have increased adjuvant potency when conjugated to antigens.[8] PAM_3cys, a TLR1/TLR2 agonist, has been linked at the N-terminus to protein antigens by their recombinant bacterial expression and demonstrated to be critical to those antigens' immunogenicity as vaccines, namely to OspA vaccine for Lyme disease.[9] In support of this mechanistic explanation, non-responding patients in a vaccine clinical trial of the Lyme vaccine were demonstrated to have deficiencies in TLR1/TLR2 function.[10] Similarly, the TLR5 agonist, flagellin, has been expressed as a fusion protein with several different microbe antigens, including recombinant West Nile virus antigen and influenza HA and M2e antigens, and has significantly improved the immunogenicity of those vaccines.[11-13]

These covalent linkage methods complicate formulation preparation, create significant limitations, require genetic or post-production modifications, and add to the regulatory burden. When agonists are linked by recombinant engineering, the ratio of linked antigen to agonist is fixed, typically at a one-to-one ratio. To the vaccines' detriment, the threshold dose of the adjuvant, above which adverse reactions are observed, becomes the limiting factor in the antigen dose that can be achieved. Chemical conjugation can be more flexible but is complicated by the difficulty of reproducibly conjugating the components at precise, desired ratios. Both recombinatory and conjugation approaches result in new chemical entities and carry with them the significant associated regulatory hurdles. Moreover, the conjugation process chemically alters the antigens, which can denature the critical protective epitopes of

FIGURE 1

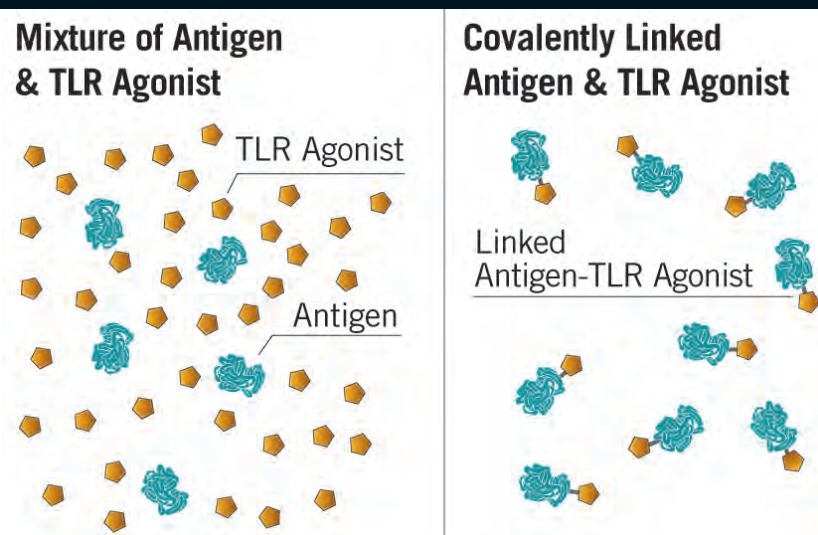

Illustration of soluble vaccine formulations with TLR agonists/adjuvants. Mixing of soluble antigens and TLR agonists can improve vaccine potency but typically requires high molar doses of the TLR agonist in comparison to antigen. The resulting high dose of adjuvant can lead to adverse reactions. Covalent linkages of antigen to TLR agonist can reduce the dose of the TLR agonist (by conjugation, fusion, protein or PAM_3cys-lipidation) in formulations and further improve the potency of these formulations. When using covalent linkages between soluble antigens and TLR agonists however, it is difficult to reduce the ratio of linked agonists to antigens below one which may limit the further optimization of the formulation's potency and safety.

the antigens and can involve conjugation linkers with their own safety concerns. What has been needed is a formulation technology that can readily link antigens and agonists at desired, varying ratios in a quick, reproducible, and flexible fashion.

VIRUS-LIKE PARTICLE & NANOPARTICLE VACCINES

Particle-based formulations have been advanced in recent years by the development of VLP and pseudovirus-based technologies, which use recombinant expression vectors in host cells to incorporate protein antigen into non-infectious VLP complexes.[14] VLP vaccine formulations have been successfully developed for human HepB and HPV vaccines, and other VLP vaccines are in clinical development for, among others, influenza and RSV.[15-16] The technology has been especially applicable for the formulations of viral vaccines using viral components that are protective antigens that self-associate/assemble into VLP structures. It has been demonstrated that these VLP vaccines often carry nucleotide-based, virus-related nucleotide sequences that are TLR agonists (TLR 7, 8, and 9 agonists) and benefit the potency of these

FIGURE 2

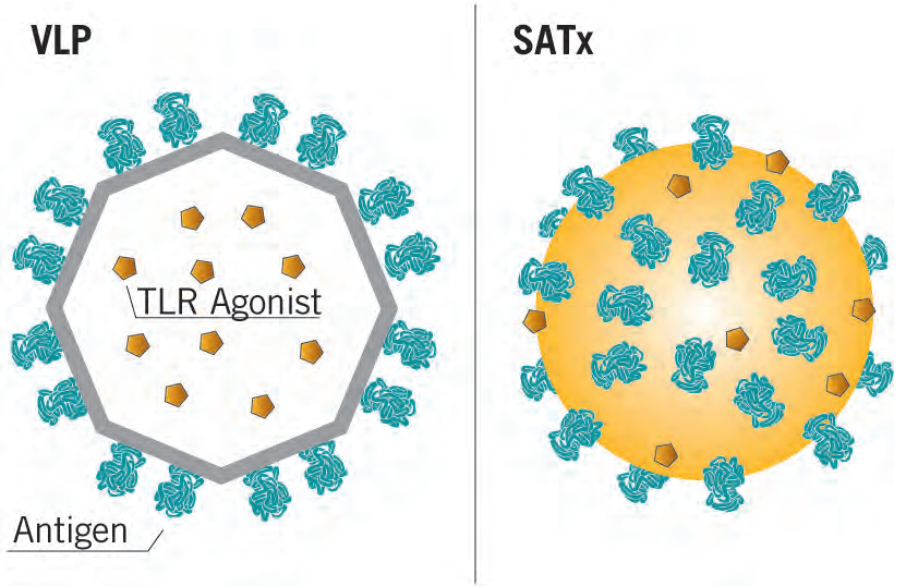

Illustration of nanoparticle based formulations. VLP products have been a successful strategy for making potent and safe viral vaccines, such as HPV and HepB. The protective viral antigen assembles into pseudoviron particles, which typically and naturally contain nucleotide-based TLR agonists, which adjuvant the product. SATx formulations are hydrophobic nanoparticles that have integrated surfactants that customize the particles' surface charges. Various antigens and TLR agonists are efficiently bound to the surfaces by electrostatic and hydrophobic binding. The dose and ratio of antigen and TLR agonists can be readily modified and optimized for both vaccine potency and safety. Results of animal studies have demonstrated that dose and ratio of TLR agonist can be decreased significantly compared to soluble formulations (Figure 1), improving the safety profile.

formulations (Figure 2).

One of the biggest challenges in developing VLP vaccines is that they depend upon the incorporation of protein antigens' genes into expression vectors that when expressed in cells as proteins, assemble into virus-like particles. This is particularly a challenge when not working with self-assembling viral protein antigens. For these non-viral targets, a portion of the non-viral protein antigen needs to be engineered into a self-assembling viral protein as a fusion protein. This limits the size of the protein antigen that can be inserted, and it depends upon the newly engineered protein antigen maintaining its protective confirmation. It takes significant development time and effort to create versions of these formulations, and they lack flexibility and control of TLR agonist content. The VLP products at the end of the manufacturing process are complex and often diverse populations of VLP structures that can be challenging to consistently manufacture, characterize, test, and release as a vaccine products.

Approaches that efficiently formulate existing purified antigens, whether proteins or other biological molecules, into nanoparticles would be useful formulation

platforms. Liposome-based formulations have been in development for many years for this purpose. The liposomes have been designed in some applications to contain and deliver vaccine antigens and immunostimulatory molecules like cytokines, lymphokines, and TLR agonists.[17] The greatest challenges for these formulations has been the long-term instability of liposomes because they are based on rather fluid, lipid membranes, and the method of linking antigens to the liposomes has often depended again on covalent-conjugation.

Particulate vaccine formulations have also be been developed and evaluated using poly(lactic-co-glycolic acid) (PLGA)-based particles. These polymer-based particles can be used to entrap vaccine formulations within the particles, which are then released as the PLGA biodegrades.[18] Vaccine antigens have also been conjugated to their surfaces for external display, though this can be a difficult process to control and reproduce. These particles also have significant limitations resulting from the necessity in using organic solvents and chemical conditions, which can denature protein antigens, making them useless as vaccines. Moreover, the PLGA particles are not stable for long-periods of time in aqueous suspensions and must be lyophilized and stored dry to prevent their natural hydrolysis before being administered as vaccines.

SURFACED ARRAYED THERAPEUTICS (SATx)

The nanoparticles developed by PSI are based on stable, hydrophobic nanoparticles that have integrated charge modifiers that give their surfaces desired electrostatic characteristics. The charge attributes of these particle can be readily modified by using different positively and negatively charged surfactants in their formulation. To these charged and lipophilic surfaces, antigens and TLR agonists can be associated by electrostatic and hydrophobic binding. The technology has now been used to successfully formulate several antigens and TLR agonists for both parenteral and mucosal vaccines.

Researchers at St. Georges University working with Particle Sciences have formulated recombinant vaccines for HIV and tuberculosis using SATx.[19,20] The binding of recombinant monomeric antigens on the surface of the nanoparticles multimerizes the antigen on the particles, which can be a strong stimulant for B cells (as previously discussed). Protective immune responses were readily induced with these formulations when the formulations were mucosally administered in mouse animal models. Particle formulations and microbes can be superior mucosal immunogens because these mucosal tissues have specialized cells, M cells, which transport particles and microbes across the mucosal membrane and into the underlying lymphoid tissues.[21] Similar vaccine formulations have also been developed as vaccines to other infectious diseases for parenteral administration.

The potency of the SATx formulations have been significantly improved by the inclusion of TLR agonists, like CpG and other agonists, on the surface of the nanoparticles. *In vitro* human lymphocyte responses to tetanus toxoid were significantly enhanced by the co-formulation of antigens and CpG on SATx.[18] These SATx formulations can be flexibly, rapidly developed to optimize the dose and ratio of antigens and TLR agonist. Results of formulations using vaccine antigens and TLR agonists have proven to significantly improve the vaccines' potencies and significantly reduced the

necessary dosage of TLR agonists in the formulations, in comparison to mixing or covalently linking these antigens and agonists. This reduction in the necessary dosage of TLR agonists thereby improves the vaccines' adverse reaction profile.

PSI has demonstrated that the technology can also be used to efficiently develop formulations that link different vaccines antigens via nanoparticles. In addition to typical protein-based vaccines, this approach can be used to develop conjugate-like vaccines that link non-proteinaceous antigens, such as polysaccharides, with both protein carrier molecules and as well as TLR agonists. To date, conjugate vaccines covalently link polysaccharide antigens to protein antigens. These conjugate vaccines provide polysaccharide antigen-specific B lymphocytes a means to bind the polysaccharide via their antibody and also interact with associated protein antigens, which facilitates needed T lymphocyte signaling. Nanoparticles carrying both the polysaccharides and carrier proteins on their surfaces should provide a more bio-mimetic function to the B lymphocytes. A number of critical infectious disease targets have important polysaccharide-based protective antigens, like S. pneumonia, H. influenza, and N. menningiditis. The development of conjugate vaccines has been key to preventing these diseases in infants because they can't immunologically respond to polysaccharide antigen alone.[22] However, conjugate vaccines are difficult and expensive to consistently manufacture. SATx could provide a new, flexible, and cost-effective alternative to covalent conjugation in developing these vaccines for human and veterinary applications.

SATx technology provides a new flexible formulation platform for the generation of nanoparticulate vaccine formulations without the limitations of previous formulation technologies that have inhibited the optimization of vaccine potencies and safety profiles. The SATx formulation platform is available to PSI clients for collaborative development projects and subsequent licensure. ◆

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BIOGRAPHIES

Dr. Robert S. Becker graduated from the University of Kansas with a PhD in Microbiology and Immunology, and Columbia University Business School with an MBA. He worked academically at the University of Illinois Chicago and Loyola University Chicago for several years in the fields of cellular and molecular immunology. He subsequently worked 21 years in what is today Sanofi Pasteur and the biotechnology company VaxInnate in leading research/development and business development roles, and an additional several years in the medical device field. In that time, he has worked on the development of numerous vaccines, formulation technologies, and drug delivery devices, including vaccines of influenza, pneumococci, meningococci, Lyme, Malaria, HPV, Dengue, pediatric combination vaccines, and intradermal delivery. He has responsibility at Particle Sciences for the growth and management of the biopharmaceutical and vaccine formulation business.

Dr. Mark A. Mitchnick founded Particle Sciences in 1991 and has been its CEO since that time. Prior to that, he was a practicing physician in New York and in a number of developing countries. In addition to his role as CEO, Dr. Mitchnick has been extensively involved in global health endeavors. He is an active member of the life sciences community, a consultant for several private equity firms, and has served as a Director for multiple therapeutic and diagnostic companies. Dr. Mitchnick holds over 20 patents related to drug delivery, diagnostics, and physiologic monitoring. He earned his BSc in Animal Sciences from Purdue University and his MD from Georgetown University Medical School. He trained in Pediatrics at The New York hospital, Cornell Medical Center, and completed the OPM program at Harvard Business School.

DRUG DEVELOPMENT
BIOSPECTRA Executive

BioSpectra: Trusted & Reliable Source for Intermediates

Headquartered in Bangor, Pennsylvania, BioSpectra has a recognized company vision to provide the most trusted and reliable source for life science intermediates. Launched in 1994, the company has grown from developing and manufacturing the first-ever Quality System Compliant versions of key biological buffers, to now also providing Zwitterionic Buffers, Carbohydrates, Excipients, Active Pharmaceutical Ingredients, and starting in Q4, Amino Acids. Offering custom solution versions of every product it makes, BioSpectra values the Quality Partnerships it forms with customers to identify and exceed expectations and requirements. Richard Mutchler, President of BioSpectra, recently spoke with *Drug Development & Delivery* about the company's unique ability to provide customers with validated, secure, and traceable intermediates that remain affordable.

Richard Mutchler
President
BioSpectra

"Clearly, the industry is finally evolving and recognizing the need to allow excipient and intermediate manufacturers the opportunity to assume the responsibility for what they sell. It is time for each manufacturer or seller of ingredients to our industry to declare the intended end use for the products he sells, to document the basis for those assurances, and to remove that responsibility from the drug manufacturers. It is time to stop asking pharma manufacturers to make drugs from chemicals that are labeled as *not for use in drug products*."

Q: For our readers who may be unfamiliar, can you provide some company background and history on BioSpectra?

A: BioSpectra was founded in 1994 with a goal to develop and manufacture the first-ever Quality System Compliant versions of key biological buffers. Following more than 300 Research and Development-scale production batches performed in our original lab in Shawnee-on-Delaware, PA, we opened a 10,000-sq-ft manufacturing facility in Sciota, PA, in 1996. During our early years, preference for the quality-system-based versions of our core products was slow to develop. However, many companies valued the exceptional consistency and purity of our materials, which were at that time, unique characteristics for those batch sizes of 200 to 500 kg. As more companies came to visit our facility, the growing interest in Quality System Compliance as the basis for our product consistency and purity became the foundation of BioSpectra's reputation. With our eyes focused on quality, we continued to manufacture Urea, Guanidine HCl, Tris, and Tris HCl through 2002 at the Sciota, PA, facility.

With the exception of direct sales to key European drug manufacturing customers, our chemicals were sold exclusively through one distributor from 2001 through 2011. During that time period, BioSpectra moved to a larger 20,000-sq-ft facility located in Stroudsburg, PA. This larger facility allowed us to

advance our quality platform. BioSpectra was able to design, install, validate, and manufacture exceptionally pure and compliant biological buffers and buffer solutions with its industry-leading, dedicated process suites for each product. Scale of production also improved to allow crystal batch sizes from 3,000 kg to 24,000 kg and solution batches of 50 L to 20,000 L.

In 2011, the exclusive distribution agreement was mutually discontinued, and BioSpectra branded chemicals became widely available to the remainder of our industry. Today, BioSpectra's in-house, contract manufacturing capabilities provide proprietary versions of its materials exclusively to many customers.

Since 2011, our quality focus has expanded to the achievement of yet higher compliance versions of our products directly by their design, validation, and manufacture to specifically satisfy end-drug use requirements. In 2012, we purchased an additional 150,000-sq-ft facility in Bangor, PA, to support our Quality expansion to include full ICH Q7 compliance for our two newest grade offerings, Bio Excipient Grade and Bio Active Grade.

Q: What products and services does BioSpectra specialize in?

A: BioSpectra manufactures Biological Buffers, Zwitterionic Buffers, Carbohydrates, Excipients, Active Pharmaceutical Ingredients (APIs), and starting in Q4 2014, Amino Acids. Custom solution versions of every product are available as well. Excipient and API versions of our core products and contract manufactured intermediates are offered upon request. BioSpectra forms Quality Partnerships with its customers through which their expectations, needs, and end-use application are defined. Written documentation of a mutually agreed upon set of compliance standards is established to successfully guide the relationship. We offer Drug Master File access for Excipient and API partners who require that additional regulatory support.

To achieve and maintain the "BioSpectra level of quality" for all of its offerings, we manage our raw material supply chain. We determine the appropriate quality attributes with the customer and perform impurity risk analyses to ensure the continued suitability of the raw materials we use in our processes. We develop a manufacturing process, validate and manufacture the material, and conclude with our in-house accelerated stability program. Additionally, BioSpectra offers a full range of particle manipulation services that includes Jet Milling and Blending performed using Q7-Compliant suites and systems.

Q: What value does BioSpectra bring to its clients? How are you different from your competitors?

A: BioSpectra has, without exception, the best designed and most compliant processes to manufacture life science intermediates. While we perhaps have the newest and largest facility in existence dedicated to these product lines, BioSpectra sets itself apart from other suppliers with the internal work culture of its employees. They are a devoted team of individuals who are committed to providing the highest quality products and services to the chemical industry and to achieving each customer's total satisfaction. BioSpectra's state-of-the-art QC Laboratory is equipped to offer safe, validated, secure, and traceable intermediates for use to protect our customers' end chemistry - all at cost-effective prices. Furthermore, we declare the end-use suitability of our chemicals on each certificate of analysis. Our direct quality relationships provide the best access and support for all regulatory and quality issues. Throughout the BioSpectra experience, our Customer Service Specialists provide attention to each customer's order processing and delivery instructions, ensuring requested product specifications, coding, and packaging requirements are met to support the timely resolution of all questions and concerns.

Q: How do you overcome the association between quality and affordability?

A: Chemicals manufactured by BioSpectra and sold directly or through our approved channel partners provide quality at the best value available. We offer US-manufactured, safe and compliant Excipients at lower prices than those of our competitors' off-shore manufactured or repackaged and "spot-tested" versions of the same materials. Because Quality is the primary requisite for all of BioSpectra's business operations and end products, the economies of scale and benefits of product consistency result in our competitive price advantage. True cost of ownership for our US-produced materials is almost always the best value financially as well.

Q: Can you tell our readers more about your newest facility?

A: The new 34-acre/150,000-sq-ft facility in Bangor, PA, is dedicated to biopharmaceutical and life science intermediates, Excipients and APIs. The facility follows ICH Q7 in its design and operations. While the facility has buildings that were built as far back as the 1700s, it is nearing completion of a total renovation, making it all new. The structure lends itself to exceptional security and stability. We have controlled storage and warehousing areas and fully independent and controlled packaging, manufacturing, particle manipulation, laboratory, and utilities in designated zones throughout our facility. In addition to our several fluid-bed dryers and custom drying systems, we have also added rotary vacuum-drying and spray-drying in this facility. Our first operational zone has five qualified manufacturing suites, each ready to manufacture any of our core products or customer-custom products. Our on-site accelerated stability and real-time stability programs also ensure the delivery of material to meet your schedule.

Q: How has manufacturing for the biopharmaceutical and pharmaceutical industries evolved in recent years? How do you keep pace?

A: BioSpectra has set the pace for quality-based manufacturing of life science intermediates since the first day it opened. Our list of "firsts" is long, but we do not focus on them. We are always focused on the next opportunity to improve end dose safety and security. Clearly, the industry is finally evolving and recognizing the need to allow excipient and intermediate manufacturers the opportunity to assume the responsibility for what they sell. It is time for each manufacturer or seller of ingredients to our industry to declare the intended end use for the products he sells, to document the basis for those assurances, and to remove that responsibility from the drug manufacturers. It is time to stop asking pharma manufacturers to make drugs from chemicals that are labeled as "not for use in drug products." Further, it is time to practice this responsibility at the correct, reasonable, and value added price-point.

Q: What are the next critical steps for BioSpectra?

A: We have a long list of upcoming Amino Acids, Carbohydrates, and other new products that we will offer in versions ranging from existing market purities to higher compliance, traceable, and validated ICH Q7 versions as Excipients and APIs. We are quickly expanding our custom solution capabilities and are planning a media prep site for 2015.

Our operational focus will also include a program to evaluate fully US synthesized versions of key Life Science intermediates, Excipients, and APIs currently available only from manufacturers or suppliers that do not offer fully ICH Q7 compliance with written support, documentation, and regulatory support. We have four products in that pipeline for US synthesis in 2015, and we are looking for new additions.

We are fortunate to have a great team, the best facilities, lots of room to grow, and strong relationships with the finest drug manufacturers in the world. In short, we will go where they direct us, and it will be BioSpectra's privilege to serve them. ◆

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Technology & Services Showcase

Analytical Support Services

ABC provides IND-enabling, registration, and post-commercialization support for the development, quality control, and lifecycle management of innovative therapies and generic medicines. Our personalized, results-based approach to development strategy is backed by decades of experience delivering GLP- and CGMP-compliant analytical testing services across all types of APIs and formulations. Through development know-how, cross-disciplinary technical expertise, and applied experience with evolving global regulatory frameworks, we help efficiently advance and manage programs for large and small molecule drugs, medical devices, and combination products. Our mission is to become a trusted extension of our client's product development teams, helping them meet the global demand for safer, more effective products. Our approach to doing business promotes relationships beyond a simple transaction. This, in turn, improves decision-making, expedites development, and reduces risk. In other words, "better insight, better outcomes." For more information, visit ABC Laboratories at **www.abclabs.com**.

Solid Oral Dosage Forms

Agere Pharmaceuticals' services include solubilization formulation design and development, cGMP analytical, and solid oral dosage forms. Solid dosage forms supported include tablets, capsules, powder for inhalation, and alternative dosage forms. Our capabilities include excipients selection, drug excipient ratios, and process development. We also support clients by preparing immediate and sustained-release forms for the clinic. In addition to characterization of unit operations, Agere offers a broad spectrum of analytical and physical measurement capabilities. Formulation development leverages our Quadrant 2TM solubilization platform, and all Agere services follow QbD guidelines. For more information, contact Agere at (541) 318-7115 or visit **www.agerepharma.com**.

Versatile DPI

Global solution provider of innovative and proven aerosol, injection, and spray delivery systems for prescription drugs, Aptar Pharma Prescription Division recently launched Twister® capsule-based Dry Powder Inhaler (DPI) with the aim to bring cost-effective drug delivery devices to pharmaceutical companies, helping them market affordable healthcare treatments to patients worldwide. Twister allows asthma sufferers to not only gain better access to medication, but also become more compliant with the treatment they receive due to its feedback design. The transparent, patient-friendly device requires three simple steps to operate: insert a capsule, twist, and inhale - and the patient will be guided by various audible and visual feedbacks confirming that the full dose has been properly delivered. For more information, contact Elisa Eschylle of Aptar at elisa.eschylle@aptar.com or visit **www.aptar.com/pharma**.

Specialty Ingredients

Ashland Specialty Ingredients offers industry-leading products, technologies, and resources for solving formulation and product performance challenges in key markets, including personal care, pharmaceutical, food and beverage, coatings, and energy. Using natural, synthetic, and semi-synthetic polymers derived from plant and seed extract, cellulose ethers and vinyl pyrrolidones, Ashland offers comprehensive and innovative solutions for today's demanding consumer and industrial applications. Ashland is a highly respected supplier of excipients and tablet film-coating systems to enable the formulation and delivery of active ingredients. Using our wide range of products, developers create reliable formulations for tablet binding, controlled-release formulations, tablet film coating, drug solubilization, and tablet disintegration applications. For more information, contact Ashland Specialty Ingredients at (877) 546-2782 or visit **www.ashland.com/ddd/pharmaceutical**.

Technology & Services Showcase

US-Manufactured Urea

BioSpectra's cGMP, US-manufactured ICH Q7-based Urea, intended for use as an Active Pharmaceutical Ingredient, will be produced in its new FDA-registered facility in Bangor, PA, in Q4 2014. Regulatory Packets, Validation Reports, and Type II Drug Master File Authorization are scheduled for contract customers of Bio Active Urea during Q2 2015. BioSpectra's Bio Active Grade Urea, Product Code UR22, will be manufactured in a qualified and validated ICH Q7-compliant API manufacturing suite as a highly purified crystal with optimum solubility, purity, and traceability. Future versions of Bio Active Urea will include liquid and spray-dried forms, both of which are currently scheduled for release in Q3 2015. For more information, contact BioSpectra at (877) 982-8333 or visit **www.biospectra.us**.

HPMC Capsules

Capsugel's Vcaps Plus HPMC (hypromellose) capsules are non-animal capsules with low-moisture content that also meet global pharmaceutical standards. A proprietary capsule-manufacturing process eliminates the need for gelling agents and delivers gelatin-like consistent disintegration and dissolution properties. The unique performance characteristics of Vcaps Plus HPMC capsules expand the range of applications for two-piece capsules. The proven properties of Vcaps Plus capsules make them an excellent alternative to gelatin or traditional HPMC capsules for optimizing delivery, performance, and stability of over-the-counter, New Chemical Entities, and off-patent products, as well as reduce development timelines. For more information, contact Capsugel at (888) 783-6361 or visit **www.capsugel.com**.

Platform Technology

CAPTISOL®

Ligand is a biopharmaceutical company that develops and acquires technology and royalty revenue generating assets that are coupled to a lean cost structure. Ligand's Captisol® platform technology is a patent protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Captisol® has enabled five FDA-approved products, including Pfizer's VFEND® IV and Baxter's Nexterone®. For licensing opportunities, call Captisol Services at (877) 575-5593 or visit **www.captisol.com**.

Biologics Development

Catalent's proprietary Gene Product Expression Technology (GPEx®) sets the standards in mammalian cell line engineering. GPEx allows rapid selection of the best clinical candidate from a group of potential molecules, providing a stable Master Cell Bank to rapidly generate proteins for clinical trials. GPEx technology can ensure genetically stable cell lines are produced 100% of the time. The advanced mammalian cell line technology in GPEx accelerates timelines, increases reliability and yield, and provides superior cell stability compared to any other method, with flexibility and unmatched versatility. Catalent provides a faster path from gene to clinic and offers high-performance cell line biologics development and biomanufacturing. Catalent boasts a new, state-of-the-art, biologics manufacturing facility in Madison, WI, allowing for batch sizes from 10-1,000 L. To learn more about Catalent's global Biologics capabilities, call (877) 587-1835 or visit **http://www.catalent.com/index.php/development/biologics/overview**.

Technology & Services Showcase

Full-Service CMO

CordenPharma is your full-service CMO partner in the Contract Development & Manufacturing of APIs, Drug Products, and associated Packaging Services for antibiotic/oncological, peptide/injectable, and highly potent/small molecule technology platforms. With multiple cGMP manufacturing facilities across Europe and the US, CordenPharma experts translate your complex ideas into high-value products at any stage of development. CordenPharma provides proprietary peptide, lipid and carbohydrate technologies for cGMP-compliant products and services to customers at competitive prices. We additionally specialize in the manufacturing and containment of highly potent peptide APIs (with exposure limits as low as 1 ng/m3), highly potent formulations (solid forms), cephalosporins & penicillins (oral & sterile), oncology drug products (oral & sterile), and packaging. Visit CordenPharma at AAPS Booth 1515 or visit **www.cordenpharma.com**.

Differentiated Injectable Drug Delivery

Credence MedSystems is focused on delivering medications safely for the benefit of our patients, caregivers, and partners. The philosophy of Innovation Without Change resonates throughout the Company and our products. It results from the team's fresh perspective and intense desire to understand the needs of both the end-user and the pharmaceutical manufacturer in the overriding goal of improving patient care. The Credence Companion Safety Syringe System offers best-in-class drug delivery along with a vastly simplified path to market for our biopharmaceutical partners. The Companion uses any pre-filled syringe and primary package components as a foundation to result in an advanced passive needle-retraction device with automatically disabling technology. Because the primary package and vendor are unaffected, the development and regulatory requirements as well as the sourcing impact are minimized for our pharmaceutical partners. For more information, contact Credence MedSystems at 1-844-CMEDSYS or visit **www.CredenceMed.com**.

Super Refined™ Excipients

CRODA

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

Design, Devices, Expertise

DUOJECT MEDICAL SYSTEMS

Duoject, founded in 1985, is a highly regarded supplier of innovative medical devices and design development services to the pharmaceutical industry. Our standard products include EZ Link, an innovative vial adapter, which has a unique safety disc that eliminates needlestick injuries and prevents the drug transfer spike being touched and contaminated prior to use; PenPrep EVO, a unique device allowing the rapid, simple, and safe reconstitution of a lyo drug vial and diluent contained in a 3-ml cartridge (once reconstituted, the drug cartridge is inserted in a multi-dose pen injector to deliver multiple injections); and VaccJect, a revolutionary alternative to a prefilled syringe fitted with a passive needle safety system (it uses a standard compact drug cartridge that optimizes cold chain transportation and drug storage(). For more information, contact Duoject Medical Systems at (877) 534-3666 or visit **www.duoject.com**.

Technology & Services Showcase

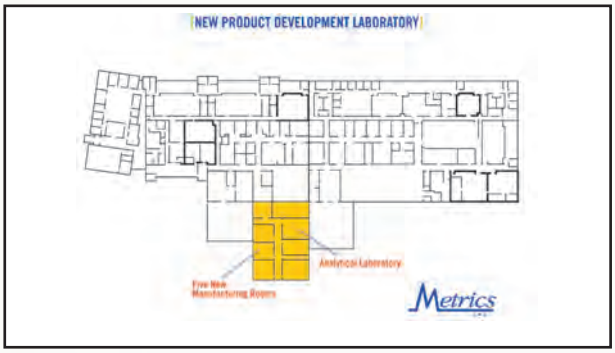
Airless Dispenser

High Efficiency Airless Dispenser (HEAD) is the combination of a metering pump including a self-sealing actuator and a pouch-bottle using LABLABO's EasyFoil technology. The result is a very precise product dispensing with the highest protection of your sensitive formulas. No evaporation, No oxidation, No microbial contamination, No desiccation, No UV degradation, and No C-C interaction. It secures precise and uncorrupted doses of product for the patient (Pump dose: 0.25 ml/3 ml; Pouch content: 30 ml/250 ml. For more information, visit LABLABO at **www.lablabo.com**.

Excipients & Technology

MEGGLE Excipients & Technology is a global leader in the manufacture of lactose for the pharmaceutical industry. Supporting supply chain security with manufacturing facilities in Europe and North America, MEGGLE offers a broad product portfolio of monohydrate, anhydrous and dry powder inhalation (DPI) lactose grades. In order to fulfill special requirements for its customers, MEGGLE offers the development of tailor-made product solutions including individual product specifications (i.e. physical, chemical, microbial parameters). In addition, MEGGLE is a pioneer in co-processing technologies and has developed highly functional excipients possessing unique qualities for directly compressible, immediate & sustained release pharmaceutical solid dosage forms. For more information contact the MEGGLE Group at (844) 4–MEGGLE (463-4453) or visit **www.meggle-pharma.com**.

Product Development Lab



Metrics is making significant investments in facilities and equipment for the benefit of contract services clients with a new laboratory to better support fast-track development of pharmaceutical products. The $1.6-million, 4,524-sq-ft facility provides maximum flexibility for early formulation and analytical method development. The facility is designed for preclinical development of early formulation prototypes and related analytical methods. In this laboratory setting, formulators and chemists will have significant autonomy to conduct development activities more quickly. Segregated from the main Metrics operations and containing fully dedicated equipment, these new processing suites have independent HVAC systems and state-of-the-art engineering controls, such as interlocking airlock doors, room air pressure differentials, high-volume room air turnover, and 100% HEPA air filtration. For more information, visit Metrics Inc. at **www.metricsinc.com**.

Innovative Packaging

Nemera is the global leader in healthcare rigid plastic packaging and devices, and provides solutions to protect and deliver pharmaceuticals. Building on its core expertise in plastic injection, injection blow-molding, and high-speed automated assembly, the company designs, develops, and manufactures innovative packaging to improve patients' health. The firm relies upon its regulatory knowledge to support our customers and manufactures in strict compliance with GMPs to meet the highest standards of quality, safety, and consistency. For more information, visit Nemera at **www.nemera.net.**

Technology & Services Showcase

Development & Manufacturing

Norwich Pharma Services is a recognized leader in full-service contract pharmaceutical development and manufacturing. Through its Synchronized Outsourced Solutions, Norwich offers customers a single source with the highest level of quality and reliability from product development to scale-up and commercial manufacturing through clinical services. By offering complete services for a product's entire lifespan, Norwich provides your project with an efficiency and consistency of service that helps bring it to market faster and more cost-effectively. For over 126 years, Norwich has built a reputation for dependable product supply and established an unparalleled history of regulatory compliance. For more information, visit **www.norwichpharma.com**.

Aseptic Filling & Lyophilization

PYRAMID Laboratories, Inc. is a Contract, Parenteral Drug Product Manufacturer and Analytical Service provider for the pharmaceutical and biotechnology industries. PYRAMID offers a wide array of services for all phases of drug development, including Aseptic Filling, Lyophilized Product Formulation & Cycle Development, Formulation & Process Development, Product Process Validation, Clinical & Commercial Vial & Syringe Fill/Finish, Clinical & Commercial Lyophilization Batches, Labeling & Packaging, Analytical Quality Control Laboratory Services, Analytical Method Development & Validation, API & Drug Product Stability Studies, and Parenteral Storage & Distribution. PYRAMID is organized along the functional lines of operations, client services, and QA/QC departments, allowing it to monitor all aspects of a client's program and oversee each program directly and efficiently with quality of utmost importance throughout all facets. For more information, contact PYRAMID at (714) 435- 9800 or visit **www.pyramidlabs.com**.

Life Science Services

SGS Life Science Services is a leading contract service organization providing clinical research, analytical development, biologics characterization, biosafety, and quality control testing. Delivering solutions for over 35 years to the pharmaceutical, biologics, and medical-device manufacturers, SGS provides Phase I-IV clinical trial management and services encompassing bioanalytical testing, data management, biostatistics, and regulatory consultancy. Additionally, SGS offers GMP/GLP services that include analytical chemistry, microbiology, stability studies, extractables and leachables, virology, cell bank and virus seeds characterization, and protein analysis. With the October opening of their Carson, CA, facility specializing in microbiology and bioanalytical testing, SGS increases its wholly owned global network of contract analytical laboratories to 29 facilities in 15 countries. For more information, contact SGS Life Science Services at (310) 8853792 or visit **www.sgs.com/lifescience**.

Wearable, Disposable Injectors

Unilife has developed a flexible, scalable portfolio of wearable, disposable injectors for the subcutaneous delivery of large-dose volume therapies with optimal patient comfort and convenience. Multiple customization options are available to address specific therapeutic, operational, branding, and patient needs, including dose volume and controlled bolus, constant or variable delivery duration rate. Each device leverages human factors data with target patient populations to provide a highly intuitive, effective, and confident user experience. Designed for seamless integration with approved manufacturing methods and primary container materials, Unilife is ready to support customer needs for the commercialization and lifecycle management of their injectable therapies. For more information, call (717) 384-3400, email info@unilife.com ,or visit **www.unilife.com**.

Technology & Services Showcase

Development Services

UPM Pharmaceuticals® is an independent provider of contract formulation development, analytical services, and cGMP manufacturing. We continue a legacy of intellectual distinction and uncompromising performance with every new project. The talent and experience of our team, our dedication to science-based formulation design, and our commitment to communication and timeliness enables us to offer the highest level of customized drug development services. Our 40,000-sq-ft main facility in Baltimore features cGMP pharmaceutical manufacturing and packaging suites as well as analytical and R&D laboratories staffed by industry veterans. Whatever form your product takes, we ensure rigorous and technically sound product characterization, methods development, and QC release. Our clients enjoy service that is highly responsive and fast with total quality management characteristic of a customer-focused business. For more information, contact UPM Pharmaceuticals at 410-843-3738 or visit **www.upm-inc.com**.

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DRUG DEVELOPMENT
SGS Executive

SGS Life Science Services: Getting Medicines to Market Quickly & Safely

Mark Rogers, PhD
Senior VP, Life Science Services
SGS North America Inc.

"There is little doubt that the most significant change in the Life Science testing market is being led by the re-focus of traditionally small molecule manufacturers and pharmaceutical companies to the area of large molecule therapeutics. By virtue of the complexity of these biological entities, this is particularly demanding for businesses in the testing market due to the number and sophistication of new and unique services required to satisfy the analytical and regulatory requirements of the large molecule sector."

With 29 facilities in 15 countries, SGS Life Science Services represents the broadest wholly owned global network of contract analytical laboratories. SGS has been providing clinical research, analytical development, biologics characterization, biosafety, and quality control testing for over 35 years to the pharmaceutical, biologics, and medical device industries. SGS offers GMP/GLP contract laboratory services that include analytical chemistry, microbiology, stability studies, bioanalysis, extractables and leachables, virology, cell bank and virus seeds characterization, and protein analysis. The company also provides Phase I-IV clinical trial management and services encompassing bioanalytical testing, data management, biostatistics, and regulatory consultancy. Mark Rogers, PhD, Senior Vice President Life Science Services at SGS, recently spoke with *Drug Development & Delivery* to discuss his company's evolutionary development and the trends it is witnessing in the analytical testing market.

Q: Can you provide some background on SGS, specifically what services are offered in North America?

A: The SGS Life Science division in North America comprises a network of five laboratories - Lincolnshire, IL, Fairfield, NJ, West Chester, PA, Mississauga, ON, and Carson, CA. Certain service activities, such as microbiology, are replicated in most of the sites allowing for high capacity and mitigation of risk. Others are specific and are performed at a single laboratory but are nevertheless offered throughout the network. The scope of testing ranges from routine, compendial methods to research and development and covers a broad variety of compound types from large to small molecules.

Q: How has the testing industry changed throughout the years for SGS?

A: The product development pipeline of the pharmaceutical industry has traditionally been small molecules; however, through the years, there has been a shift toward a greater portion of the pipeline being in biopharmaceuticals. SGS realized this, and thus, in 2006, opened a laboratory in Wavre, Belgium to develop biologics testing. In 2010, SGS completed its acquisition of the M-Scan group, specializing in biologics characterization and has since developed specific, large molecule testing services in a number of the existing, traditionally small molecule, SGS laboratories. Earlier in 2014, SGS also introduced new services for the preformulation and stability testing of biologic products.

Q: What are some of the biggest challenges in the testing industry?

A: As in any business, there are challenges that are unique to the specific industry and those that are common to all. In the field of Life Science testing, responsiveness in terms of capacity and capability are a concern. For instance, a client may have an unexpected and immediate need for a unique test or expertise with which a contractor may have only limited experience. Therefore, as a service provider, we must anticipate the needs the industry may have and maintain the necessary expertise that can be developed to meet customer requests and potential regulatory requirements. For example, as part of the new preformulation and stability services, SGS is able to design and execute shipment excursion studies involving risk-based design using automated temperature and humidity cycling. Data from these studies can also be used to support formulation, forced degradation, and stability studies. Additionally, maintaining the same level of service relationship with both large and small clients, who often have very different demands on the service, is also a challenge in terms of business development and management strategies. Finally, combining strong growth while preserving quality is often difficult but essential in this heavily regulated industry.

Q: How is SGS uniquely qualified and able to address these challenges?

A: The operational challenges, such as those involving rapid changes in demand for capability or capacity, are very well addressed within SGS by utilization of the Life Science Services laboratory network. Sudden, often short-term demands for increased business are moderated by the ability to allocate the work to more than one site. Business development is structured in a way that successfully manages a broad range of clients and their needs by layered teams of specialists that are able to work collaboratively on local, regional, and global levels. Within SGS, significant emphasis is placed on quality. This attribute is recognized as critical throughout all aspects of the network and, under leadership from the business managers, is assured despite the pressures often encountered during strong growth.

Q: You recently had a press release on an investment in a new laboratory in California. What is the significance of this new laboratory for SGS?

A: The laboratory in California provides SGS with a presence on the West coast in a region of significance for pharmaceutical and biopharmaceutical testing services. This new laboratory will expand the current capabilities of SGS, offering bioanalytical testing, which is currently only performed in our European laboratories. While the bioanalytical services will be new to North America, we will be able to leverage the expertise from our sites in Poitiers, France, and Wavre, Belgium, where SGS has over 700 validated methods to date. Furthermore, the microbiological aspect of the California service offering provides a local presence to those clients who require a very rapid sample processing time. In this instance, the geographic proximity will certainly be a benefit to the clients.

Q: What makes SGS unique as an outsourcing partner?

A: SGS Life Science Services offers a truly integrated network of laboratories able to respond very quickly to the changing demands of the testing market. The network is a seamless organization, providing clients access to unparalleled expertise in a broad range of technical areas. The scope of services, from high throughput routine tests to in-depth development and validation, requires different business strategies, readily applicable in a network, such as SGS, and providing the client with ideal execution of their particular testing needs.

Q: Where do you foresee the industry heading, and how is SGS poised to handle emerging needs?

A: There is little doubt that the most significant change in the Life Science testing market is being led by the re-focus of traditionally small molecule manufacturers and pharmaceutical companies to the area of large molecule therapeutics. By virtue of the complexity of these biological entities, this is particularly demanding for businesses in the testing market due to the number and sophistication of new and unique services required to satisfy the analytical and regulatory requirements of the large molecule sector. SGS has adapted quickly to these needs by strategic investment within its existing laboratories and by acquisition. More specifically, the increasing pressure for biosimilar development and manufacture in the US will inevitably result in a surge of demand for testing of such molecules. SGS has already taken measures to develop analytical platform methods to address such a challenge and a marketing campaign to raise the profile of SGS in these services. ◆

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PREFILLED SYRINGE STERILIZATION

NO_2 Sterilization: A Flexible Solution for Prefilled Syringes

By: Evan Goulet, PhD, and Elizabeth Robbins

INTRODUCTION

First patented 40 years ago, prefilled syringes have experienced tremendous growth alongside the increased development of large molecule drugs. The injectable drug delivery market is second in size only to that of oral medication, and prefilled syringes constitute one of the fastest growing segments of that market.[1] As opposed to their glass vial counterparts, prefilled syringes provide a cost-effective and user-friendly delivery system for a controlled dose of a biologic or drug product. With products that are intended for use in ophthalmic applications or administered in the sterile field of the operating room, it is often necessary to perform a sterilization or decontamination operation on the exterior surfaces of the syringe while in a sterile barrier package. With temperature-sensitive drugs or biologics, this can present challenges for manufacturers.

Today, the most commonly employed methods for sterilization are: steam, ethylene oxide (EO), and gamma radiation. These methods have served the market well for many years, but as drugs and delivery devices have advanced, some limitations have become apparent. Sterilization with traditional methods often requires exposure to elevated temperatures or damaging radiation, which may lead to degradation of the drug product or container closure materials. Additional concerns include leaching of sterilant residuals from the stopper, the duration of the process, and the costs of sterilization.

Nitrogen dioxide (NO_2) is a well-documented and researched gas. Sterilization with NO_2 gas can provide a solution to some of the limitations presented by existing options. It can also provide the process flexibility to manufacturers that will support continued innovation and growth in the prefilled syringe market. Noxilizer, Inc. designed the Noxilizer RTS 360™ Industrial NO_2 Sterilizer that provides surface sterilization of prefilled syringes with a range of material compatibility and low levels of residuals using its rapid, room-temperature process.

CURRENT STERILIZATION OPTIONS FOR PREFILLED SYRINGES

Sterilization of prefilled syringes today is predominantly accomplished using steam, EO, or gamma radiation. While these methods are well established, their limitations could impede innovation and progress in the pharmaceutical and biotechnology industries. More than 60% of new drug products being developed today are biologics, such as protein therapies.[1] This rapid rise in biological drug development is expanding the market for new sterilization technologies that can overcome the limitations of current methods.

No single sterilization method will be compatible with every product on the market. Steam sterilization has been

around for more than a century and is well understood in both industrial and hospital settings. EO has a long track record with the broadest material compatibility, and gamma radiation offers a low-temperature option. Each of these methods has specific weaknesses with respect to sterilization of prefilled syringes. These weaknesses, discussed further, were the driving force behind the development of NO_2 sterilization.

At present, steam sterilization is the primary method employed for sterilization of glass prefilled syringes containing heat-stable products, such as saline. However, because it involves both very high temperature, typically 121°C, and pressure, it is not well suited to sensitive biologics and drugs. Further, more and more companies are looking to alternative plastic materials, like cyclic olefin copolymers (COCs), and fluoropolymer coatings to minimize any leaching or particulate interaction with the solubilized drug and patient.[2] Most of these new plastic materials cannot be exposed to high temperatures without experiencing degradation.

EO sterilization presents an alternative to steam sterilization for the external surfaces of prefilled syringes. However, EO also presents its own challenges. Although EO does not use the high temperatures of steam sterilization, it still requires temperatures in the range of 40°C to 60°C, and a relatively deep vacuum in order to achieve sterility. This can have an adverse effect on temperature-labile products, and the vacuum can cause unacceptable stopper movement due to pressure changes.

TABLE 1

Safety-Related Property	Nitrogen Dioxide	Ethylene Oxide
Color	Reddish-Brown	Colorless
Odor Threshold	0.1 ppm	200-400 ppm
OSHA PEL	5 ppm	1 ppm
NFPA: Health	3	3
NFPA: Flammability	0	4
NFPA: Instability	0	3

Comparison of Safety-Related Properties for NO_2 & EO

Drug manufacturers and researchers have long expressed concerns over the carcinogenic nature of residuals from the EO sterilization process.[3] The EO process can require lengthy aeration phases (9 to 17 days), often at elevated temperatures, to remove residuals from plastic syringes.[4] The lengthy aerations may compromise drug integrity or manufacturing efficiency. Another issue with EO is sterilant ingress, the diffusion of the sterilant past the container closure system into the product itself, which can lead to unacceptable levels of residuals within the drug product causing modifications to chemical structure and product activity.

EO sterilization also presents significant manufacturing and operator concerns. The cycle requires pre-conditioning and post-cycle aerations, which can lengthen the turnaround time considerably. Adding to this is the drawback of having the EO process performed off-site, turnaround time can extend to 7 to 25 days, depending on the product. The EO process also involves health and safety concerns, with operators at risk of exposure to highly flammable, carcinogenic, and cytotoxic chemicals and residuals during routine operation and disposal.[5] Refer to Table 1 for a comparison of the safety-related properties of EO and NO_2.

Another sterilization option is gamma radiation. Gamma does not require long aeration times and has relatively good materials and drug compatibility if a minimal radiation dose can be employed. This restriction can create cost concerns for smaller manufacturers as the entire process leading up to the final sterilization step must be done using aseptic processing in at least a Class 100 facility in order to be able to use a Bioburden Approach to process validation as opposed to the industry-accepted Overkill Approach. Additionally, gamma radiation is not ideal for aqueous drug products because it can produce toxic free radicals in the solution that can result in decreased drug activity. It can also break down preservatives used in many drug

FIGURE 1

Noxilizer RTS 360™ Industrial NO_2 Sterilizer Integrated Into a Prefilled Syringe Process

solutions that are essential to maintaining stability and shelf-life of the product. Gamma radiation has also been proven to interact with lubricants found in plastic syringes.[6,7] Lastly, the facility cost and mitigating the risk of exposing the operators to radiation must also be considered.[8]

Unique sterilization methods, such as Noxilizer's NO_2 sterilization process, offer a much-welcomed alternative to companies working to sterilize drugs delivered via prefilled syringes or delivery systems.

NOXILIZER'S STERILIZATION TECHNOLOGY FOR PREFILLED SYRINGES

Noxilizer's advanced room-temperature sterilization process uses NO_2, a well-researched gas, in combination with humidity to inactivate resistant microorganisms and deliver sterile product. The FDA recommends adding an adjunct process, or additional sterilization step, to "increase the level of sterility confidence" when aseptic processing is used in drug manufacturing.[9] This is especially true for products that are intended for use in ophthalmic applications or in the sterile field of the operating room. NO_2 gas is a surface sterilant that does not penetrate the container closure system and results in low surface residuals. The capability to sterilize at room temperature is fundamentally important because the rate of chemical reactions is approximately doubled for every 10°C rise in temperature. Maintaining lower temperatures ensures that any reactions that might occur with the product, such as denaturation and agglomeration, are minimized.

NO_2 is a non-condensing gas, and as such, it can be an excellent sterilization choice for lumens, needles, and other challenging geometries in comparison to condensing vapor systems.[10] Coupled with the ability to sterilize with low humidity and temperature, this gives NO_2 a distinct advantage when considering sterilization of combination medical devices and surface sterilization of the final product.

Noxilizer's NO_2 technology is especially well suited to, and can be conveniently installed as, an adjunct process for products that require surface sterilization (Figure 1). By providing solutions to the challenges presented by steam, EO, and gamma sterilization, NO_2

FIGURE 2

A Plas-Tech Engineering Prefilled Syringe Made With a Cyclic Olefin Copolymer (COC).

Photo courtesy of Plas-Tech Engineering, Inc.

can help broaden the horizon for use of all types of prefilled syringes, including dual-chamber and combination devices, as the drug delivery system of the future.

NO_2 works as an oxidizer that inactivates microorganisms through degradation of DNA, providing a sterility assurance level (SAL) of 10^{-6} at relatively low gas concentrations. Biological indicators for the NO_2 sterilization process consist of spores of *Geobacillus stearothermophilus*, which is the same organism used for steam sterilization.

A recent study, performed in the Noxilizer lab, demonstrated a 6-log reduction in the population of biological indicators placed next to the plunger rod in the barrels of water-filled COC syringes. The syringes, along with thermoplastic elastomer tip caps and stoppers, were provided by Plas-Tech Engineering, Inc. of Lake Geneva, WI (Figure 2). For the study, they were packaged in Tyvek-Mylar pouches. The exposure used in the study employed minimal vacuum (less than 1 psig) to deliver 10 mg/L NO_2 and 75% RH for a dwell time of 45 minutes. Including a 30-minute aeration phase, the total cycle time was 90 minutes.

A cycle that was 50% more aggressive in both concentration and exposure time was used to characterize sterilant ingress in the COC syringes. When tested via ion chromatography, water from the syringes exhibited residual nitrate levels that were below the limit of detection (2 µg/mL). When determined via a pH measurement method, the nitrate residuals were 0.002 ppm, which is 100 times below the Water for Injection (WFI) limit of 0.2 ppm stated in the European Pharmacopoeia.[11]

Noxilizer's demonstrated ability to sterilize the exterior surfaces of polymeric prefilled syringes using a rapid cycle, minimal vacuum, and a truly room temperature process suggests that NO_2 sterilization is an ideal solution for manufacturers of sensitive biopharmaceuticals. Table 2 provides a comparison of NO_2 sterilization with EO. In addition to the advantages outlined in Tables 1 and 2, the financial benefit of using NO_2 instead of EO could also be substantial (up to 40% to 60% cost savings). NO_2 sterilization equipment is significantly less expensive and does not require extensive facility modifications to be installed. This would allow manufacturers currently using contract sterilization to move their sterilization process in-house, thereby reducing costs and turnaround times. NO_2 gas offers a faster and more compatible option to companies looking to manufacture their products in prefilled syringes.

The RTS 360™ can be easily installed in any manufacturing setting with a 240-VAC, single-phase connection. No other facility modifications or specialized equipment, such as an EO abator, are required. After exposure, the exhaust gases from the NO_2 sterilization process are passed through an on-board scrubber, which neutralizes the sterilant, rendering the exhaust safe for the operator and the environment. The spent scrubber material is a solid, landfill-safe material. This makes

TABLE 2

	Noxilizer RTS 360™	Typical EO System
Estimated Average Cycle Time	120 minutes	12-18 hours
Capacity	360 Liters	2200 Liters
Pre-conditioning	No	Yes
Estimated Aeration Time	60 minutes	9 days [4]
Relative Humidity	Low to High (30%-80%)	High (70%)
Vacuum	Minimal	Yes
Operating Temperature	Room Temperature	40°C-60°C
PFS Material Compatibility	Yes	Yes
Sterilant Ingress	Below WFI limit	Common Issue
Residuals	Low non-cytotoxic non-carcinogenic	Low cytotoxic carcinogenic
Operator & Environmentally Friendly	Yes	No
Manufacturing to Release Time	On-site, immediate release	Off-site, 7-24 day turnaround

Comparison of NO_2 & EO for Prefilled Syringe (PFS) Sterilization

FIGURE 3

The Patented Noxilizer RTS 360™ Industrial NO_2 Sterilizer

bringing sterilization in-house easy and safe, resulting in faster turnaround times.

For those manufacturers who would prefer to have sterilization done off-site, Noxilizer offers contract sterilization services in ISO 13485-certified facilities. Noxilizer's microbiology and materials science expertise is available to develop and validate processes specific to a customer's product needs.

ADDITIONAL APPLICATIONS OF NO_2 STERILIZATION IN THE SYRINGE MANUFACTURING PROCESS

While NO_2 gas provides an excellent option for surface sterilization of the final prefilled syringe product, there are also clear benefits to integrating NO_2 sterilization into other steps of the prefilled syringe manufacturing process. With the same NO_2 technology, Noxilizer has developed the NOX FLEX™ Rapid Biodecontamination System, which provides significant gains in cycle times versus current technologies. Noxilizer has also designed an in-line sterilization system that will allow manufacturers of syringe components to efficiently sterilize product without having to send truckloads of syringe tubs to EO contract sterilization facilities. A similar system can also be used to decontaminate the exterior surfaces of the syringe tubs prior to entering a filling isolator without the concern of shadowing that arises with e-beam. In a related area, Noxilizer has already completed a global supply agreement with Weiler Engineering, Inc. for an NO_2 decontamination system for their Blow-Fill-Seal aseptic filling equipment. ◆

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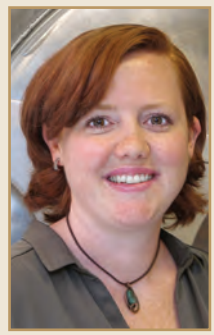
BIOGRAPHIES

Dr. Evan Goulet is Director, Sterilization Operations at Noxilizer, Inc. In this capacity, he works with customers to develop NO_2 sterilization process validation plans for medical and drug delivery devices. Dr. Goulet earned his Bachelor of Materials Engineering from Auburn University and his PhD in Materials Science from the University of Pennsylvania. He can be contacted at egoulet@noxilizer.com.



Elizabeth Robbins, since joining Noxilizer Inc. in 2009 as a Senior Microbiologist, has expanded her microbiology expertise through development and testing of their novel sterilization process. Ms. Robbins earned her BS in Biotechnology in 2006 from Stevenson University in Baltimore, MD. She can be reached at lrobbins@noxilizer.com.

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Lead Me, Follow Me, or Get Out of My Way

By: John A. Bermingham

The original quote, "lead, follow, or get out of the way" is attributed to Thomas Paine. The title of this article is a quote attributed to General George S. Patton. General Patton's modification of Thomas Payne's original quote is typical of the General, and one of the reasons that I have always admired him for most, but not all, of the things he is known for.

General Patton has been revered and chastised for his leadership tactics and style. He was very direct, open, honest, abrasive, dictatorial, arrogant, overbearing, and no-nonsense, just to name a few. But I would rather report to someone like General Patton than other leaders I have known and, unfortunately, reported to.

I believe that not knowing where you stand with the person that you report to is a terrible situation to be in. He or she never gives out "atta boys" or "atta girls" when something is done well or a sit down for a discussion when something is not done well. There is a lack of coaching and mentoring. Maybe you get a brief smile when something goes well or a grimace or frown when something doesn't go well, but not much else.

People who act in this manner are really doing a disservice to themselves and to the people they manage. They create a culture of negativism between themselves and their people because when a person doesn't know where they stand with their boss, the person tends to set up psychological defenses against his or her boss. This eventually causes an abrasiveness to develop between the two people. This situation always gets worse over time and generally ends badly.

As a manager of people, it is critically important that you not let this happen to you. When things are going well, it is easy to sit down with someone and talk about a job well done and heap praise on them. But when things are not going well, while difficult to address, it is something that all good managers do by sitting down with their people to address the issue.

This is not an opportunity to chastise someone, belittle them, and pound them into the ground. That's what bad managers do. Rather, this is an opportunity to coach and mentor this person and help them become much better in their work responsibility. They will not just know where they stand with you, but will develop a loyalty to you and a strong effort to meet your needs in their work responsibility.

If, after a period of time, things do not work out, then you can make a change with a clear conscience, and the person involved will certainly not be surprised. When I encounter this type of situation, I often think about General George Patton. Not the General Patton who was the abrasive, dictatorial, arrogant, fist-pounding leader but the General Patton who was decisive, communicative, and very clear leader on what he wanted and expected. ◆

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Biography

John A. Bermingham is currently the Executive Vice President & COO of 1st Light Energy & Conservation Lighting, Inc. He was previously Co-President and COO of AgraTech, a biotech enterprise. Previous to that, he was President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. More previously, he was President & CEO of Alco Consumer Products, Inc., Lang Holdings, Inc., and President, Chairman, and CEO of Ampad, all of which he turned around and successfully sold. With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona, Corporation, and Rolodex Corporation as well as turning around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group, and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 years in the US 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 graduated from the Harvard University Graduate School of Business Advanced Management Program.


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Drug Development & Delivery
SPECIAL FEATURE - Prefilled Syringes & Parenteral Contract Manufacturing - Product Differentiation Is Critical
After oral drug administration, parenteral delivery is the second most applied route of drug administration. A steady increase in the number of parenteral drugs has led to rise in demand for various advanced drug delivery devices that ensure ease of administration as well as cost containment. Prefilled syringes
stitute one of the fastest growing segments of the in
elivery devices market. The various advantages
ed syringes over conventional delivery sys
nd ampoules, have been the primary found
ss to date and are expected to continue to
during the forecast period 2013 to 2019.1
s include ease of administration, improved safety,
of contamination, and accurate dosing. Estimates show that the global prefilled syringes market is likely to achieve sales of $6.9 billion by 2018, growing at a compounded annual growth rate of 13.8% from 2012 to 2018.2
Depending on the type of material used to manufacture the syringe barrel, prefilled syringes are available mainly in two types, glass prefilled syringes and plastic (polymer) prefilled syringes.
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